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Infections Today

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OF NORTH AMERICA

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THE MEDICAL CLINICS OF NORTH AMERICA

Nationwide Number

Infections Today

CHARLES H. RAMMELKAMP, M.D., D.Sc.
Guest Editor

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Endocrine, Metabolic and Nutritional Disorders

March, 1963—*from Lahey Clinic*

Difficult Diagnostic Problems

May, 1963—*from New York*

The Liver and Its Diseases

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Symposium on Infections Today

FOREWORD

THE ENTIRE FIELD of disease as it relates to infectious agents and immunology has exploded with activity, and observations now being made in the laboratory will result in the development of new methods of prevention and treatment. Two decades ago the interest in immunology and infection reached a low ebb. Immunological procedures were utilized primarily as a diagnostic aid and were not widely employed as a tool to study the pathogenesis of various disease processes. Following the introduction of the sulfonamide drugs and penicillin, physicians were satisfied that the ultimate antibacterial agents were available. Shortly thereafter, with the introduction of effective therapy for tuberculosis and broad-spectrum antibiotics, interest in the infectious diseases declined again and young investigators turned their efforts toward other fields.

The dramatic change in attitudes observed today is largely due to two new developments. First, the use of tissue culture techniques for the study of viruses has resulted in the identification of large numbers of new infectious agents, some of which produce syndromes now recognized by clinicians as distinct diseases. In the area of viral respiratory infections alone, the number of new agents which cause disease is so great that frequent reviews, such as appear in this issue, are necessary. Since treatment of most viral infections is not specific, great interest in immunization is developing. The ease of growing pure viruses in large quantities, and the data accumulating concerning the duration of immunity indicate that many viral infections may be prevented by immunization. The question facing us today and in the immediate



CHARLES H. RAMMELKAMP, M.D.

future will be the proper use of the multiple immunization procedures which will be made available to the physician.

The second area of rapid expansion of knowledge is related to newer immunological techniques which are being applied to a wide variety of diseases of both infectious and noninfectious nature. It is apparent that future editions of *The Medical Clinics* will describe these developments, for they will play an important role in the treatment and control of a wide variety of diseases.

Finally, because of these developments, all areas of infections are coming under close scrutiny, for, as the population ages, infections remain an important cause of death. The role of preventive measures in such populations must assume greater emphasis. There is increasing interest in the protection of the hospitalized patient against infection with staphylococci and other organisms. Concepts of isolation and antisepsis will change, for the present procedures inadequately control infections in the aged or in patients admitted to our hospitals.



Guest Editor

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The Use of Amphotericin B in Blastomycosis, Cryptococcosis and Histoplasmosis

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THE INTRODUCTION of a reasonably satisfactory antifungal agent into clinical medicine represents another forward step in the pathway marked by the sulfas, penicillin and streptomycin. Amphotericin B is the first even reasonably effective antifungal therapeutic agent for treatment of all the deep mycoses. The history, dosage, toxicity and methods of administration of this antibiotic will be discussed in the article on coccidioidomycosis by Dr. William A. Winn, which follows. The present paper will be limited to a discussion of the three systemic mycotic diseases listed in the title.

THE USE OF AMPHOTERICIN B IN BLASTOMYCOSIS

As emphasized by Curtis and Harrell in 1961,¹⁴ blastomycosis is a fungus infection which merits therapy once the diagnosis is firmly established. This is because no mild cases have been reported and the mortality rate in large series as reported by Martin and Smith³³ was 93 per cent within three years of diagnosis.

Blastomycosis appears to be the most readily responsive of the systemic mycoses to therapy and was the first for which therapeutic agents were made available. Colbert et al.¹² first reported that propanimidine had a definite effect in blastomycosis. The use of the diamidines, mainly stilbamidine, was first reported in 1951 by Schoenbach et al.⁴² This drug was toxic particularly to the trigeminal nerve and was replaced later by 2-hydroxystilbamidine, which has a much lower incidence of side effects.

Table 1. Results of Treatment of 135 Cases of North American Blastomycosis Gathered from the Literature*

(Included are 81 Cases Treated with Diamidine, 39 Cases Treated with Amphotericin B, and 15 Cases Treated with Amphotericin B After Failure of Diamidine Therapy.)

RESULTS	TREATMENT			
	Diamidines	Amphotericin B	Both	
Arrested.....	No.	%	No.	%
Arrested.....	54	67	27	69
Improved.....	12	15	9	23
Unimproved.....	10	12	1	3
Died.....	5†	6	2	5
TOTAL.....	81		39	15

* Modified from Sutliff.⁴⁹

† One patient died of cause other than North American blastomycosis.

There is still considerable controversy as to the relative efficacy of 2-hydroxystilbamidine and amphotericin in the treatment of blastomycosis. Sutliff in 1961⁴⁹ published a comparison of these two agents in 135 cases of North American blastomycosis from a review of the literature. Table 1 is reproduced from that report. It is noted that among 81 cases approximately 82 per cent were arrested or improved with the diamidines, in contrast to 92 per cent with amphotericin. Most striking, however, are the 15 cases which were 2-hydroxystilbamidine failures and were subsequently treated with amphotericin. In 13 of these improvement occurred under amphotericin therapy.

Although 2-hydroxystilbamidine appears to have less primary toxicity, it is not devoid of serious side effects. Wigger⁵⁷ reported a fatal reaction to 2-hydroxystilbamidine in the form of liver toxicity. It can, however, be given with much less fear of immediate reaction than amphotericin, but with the knowledge of fewer satisfactory results and a greater percentage of recurrences.

Amphotericin B has been widely used in blastomycosis. Sutliff,⁴⁹ in Table 1, reported its use in 54 cases. Curtis and Harrell¹⁴ report better than 80 per cent cures with amphotericin. They also report that one can expect 10 to 15 per cent relapses even with amphotericin treatment, and they stress that the most difficult cases to treat and the most prone to relapse are those which appear to have a poor immunologic response, as evidenced by negative skin tests and positive complement fixation tests. The average total dose employed in the earlier reports approached 1 gram of amphotericin. Later experience, however, indicates that larger dosages are preferable and Seabury,⁴⁴ Curtis and Harrell¹⁴ and others feel that a total dosage of approximately 2 grams of amphotericin should be given. If relapses occur, re-treatment is indicated and the response is usually as satisfactory as on primary treatment.

Recent correspondence with various experts in the field and review of the literature subsequent to Sutliff's article⁴⁹ reveal that about half favor the use of amphotericin to the exclusion of the stilbamidines^{1, 4, 21, 45, 52} and the other half prefer to treat primarily with 2-hydroxystilbamidine, reserving amphotericin for the recurrences which follow in about one-third of the cases.^{30, 44, 46} All agreed that cases with extensive involvement or rapid progression or those in whom poor immunologic response was evidenced by negative skin test and high titer complement fixation test should receive primary treatment with amphotericin.

Most of the cases of blastomycosis are first diagnosed in the disseminated form; that is, with skin, bone or meningeal lesions. The skin and bone lesions seem to respond perfectly satisfactorily to therapy, the meningeal lesions somewhat less satisfactorily. Carmody and Tappen in 1959⁹ summarized 19 cases of meningitis from the literature, all of which were fatal, and reported one cure with amphotericin. Loudon and Lawson³¹ reported a further case in 1961 with improvement and relapse several times after treatment with amphotericin totaling 2.47 grams. This patient has remained well for two years despite transient paraplegia due to the intrathecal injection of amphotericin.

Intrathecal injection of amphotericin has only rarely been employed in blastomycotic meningitis, but based on the experience reported with cryptococcal and coccidioidal meningitis, its use should be seriously considered. Other organs involved in dissemination are the prostate and the adrenal glands with the production of Addison's disease.^{2, 7}

The problem faced by the clinician in the treatment of blastomycosis is whether to treat with amphotericin, which gives a surer result and more permanent cure, with less danger of recurrence, or to treat with 2-hydroxystilbamidine, which has less toxicity, slower cure and more recurrences. There appears to be no difference of opinion that amphotericin be employed in the treatment of the severe or progressive cases or those with meningitis.

Amphotericin B appears to be the drug of choice in South American blastomycosis as reported by Sampaio,⁴¹ who treated 61 cases. There was much less tendency for relapses to occur than with the sulfonamide treatment of this disease.

USE OF AMPHOTERICIN B IN CRYPTOCOCCAL INFECTIONS

Cryptococcal infection of human beings has a clinical significance similar to that of blastomycosis; namely, once the disease is clinically recognizable it calls for active and urgent therapy. The reason for this is explained in the fact that the *Cryptococcus* has a tendency to migrate to the meninges and there cause a usually fatal meningitis. Even where the cryptococci are apparently localized to the skin or the lungs, present clinical concepts require that immediate therapy be instituted to prevent its subsequent dissemination to the meninges, which appears to occur almost invariably. Pulmonary cryptococcosis may be of either the nodular or pneumonic variety and is frequently not diagnosed until after surgical interference. If the diagnosis is established promptly after

surgery it is recommended that therapy be instituted to prevent dissemination to the brain. In such cases approximately a month's therapy, or 1 gram of amphotericin, would appear to be satisfactory unless complications develop.

A similar course of therapy would appear indicated in cryptococcal infections of the skin where no evidence of other infection is found. Therapy here should be continued until the lesion has completely disappeared, even though this requires the administration of more than 1 gram of amphotericin B. In both the pulmonary and cutaneous varieties, observation of the patient should be carefully maintained for a long period of time for recurrences.

Cryptococcal meningitis has long been known as a serious and ordinarily fatal disease. The average length of time from diagnosis till death in over 300 cases reviewed by Littman²⁹ was six months. In the 132 cases followed by Carton,¹⁰ 92 per cent of the patients were dead within two years of the diagnosis. While average survival periods are short, it is well known that an occasional patient may survive for years without therapy.

Although many therapeutic agents have been tried in cryptococcal meningitis, only amphotericin B has proved therapeutic value. The first case treated with amphotericin was in 1957, by Applebaum and Shtokalko.³ The patient received approximately 4.2 grams by the oral and intravenous routes and his course was satisfactory. In reviewing the therapy of cryptococcal meningitis with amphotericin, it is immediately apparent that adequate dosage is of extreme importance. Unless sizable amounts of drug are introduced into the patient, the chances of relapse are great. Louria³² reviewed the results of 69 cases of cryptococcal meningitis from the literature in which 500 mg. or more of intravenous drug were employed. Fifteen, or 22 per cent, of these patients were classified as cured, 45 per cent as improved, and 33 per cent as failures; that is, failed to improve, relapsed or died. Many of these cases of unsatisfactory results, however, must be classed as inadequately treated in terms of our present knowledge.

Evans¹⁷ has analyzed the results of 22 cases treated with amphotericin at this Station. The results highlight the important factors in the treatment of cryptococcal meningitis. All cases were confirmed culturally. There were six females and 16 males. Seven of the patients had complicating illnesses. Two patients had arthritis, with steroid therapy; two had tuberculosis, and one of these also had Hodgkin's disease. Other patients had diabetes mellitus, agammaglobulinemia and histoplasmosis. Half of the cases had been followed for one year or more. There have been eight deaths in this group, four of which occurred during therapy with amphotericin B. Six of the original 22 patients have experienced relapses after their first course.

It appears that age and dosage are two of the critical factors in survival in cryptococcal meningitis. Reference to Table 2 shows that only one of ten patients died who were under 50 years of age, whereas the disease was fatal in seven of 12 patients who were over 50 years. In the same table it is seen that six of ten patients who received less than 2 grams of amphotericin died; whereas only two of 12 patients receiving more than

Table 2. Relation of Age and Dosage of Amphotericin B to Survival

AGE	DOSE		DEAD /TOTAL
	< 2 gm.	> 2 gm.	
< 50	● 000	000 000	1 / 10
> 50	● ● ● ● 0	● ● 0 000	7 / 12
DEAD /TOTAL	6 / 10	2 / 12	8 / 22

O - LIVING ● - DEAD

2 grams died. Other factors of importance are the continuation of treatment until not only the cultures but also the smears of the spinal fluid are negative. All seven patients with positive smears at the termination of therapy relapsed and five of the seven died. Another factor was the clinical state of the patient at the time of diagnosis. Those in a coma had a poor prognosis regardless of the amount of therapy.

The failure of amphotericin to readily cross the blood-brain barrier has raised the question of intrathecal treatment with this drug.²⁸ It is our present practice to recommend intrathecal therapy in patients who are comatose or semicomatose on admission or who have severe evidence of meningeal irritation. This intrathecal injection accompanies the intravenous administration and is performed every other day or twice a week. Ordinarily after a period of several weeks of therapy the intrathecal injections can be discontinued and the treatment carried on by the intravenous route. However, in those patients who fail to clear the spinal fluid by culture after one month, or by culture and smear after two months of therapy, consideration should be given to intrathecal administration or possibly even intracisternal administration as recommended by Dr. Winn in the accompanying article.

In summary, it appears necessary to treat every patient in whom systemic cryptococcosis is diagnosed, and particularly those who already have shown the onset of meningitis. These individuals should receive not less than 2 grams of amphotericin by the intravenous route. Accompanying intrathecal or intracisternal injections should be instituted in all patients who are seriously or critically ill or who fail to respond within a few weeks to the intravenous medication. In patients whose reaction to intravenous injection is excessive, intrathecal or intracisternal injection alone may be substituted.*

* Spickard et al. (Ann. Int. Med. 58: 66 [Jan.] 1963), in an article which was seen after this manuscript was submitted, feel that the presence of complicating diseases was more important than dosage in failure with amphotericin therapy. They recommend intrathecal therapy only for relapses or patients intolerant to the intravenous route.

THE USE OF AMPHOTERICIN IN HISTOPLASMOSIS**Acute Pulmonary Histoplasmosis**

As is now well recognized by most clinicians, pulmonary infection occurs almost invariably with histoplasmosis. A large percentage of these cases are self-limited and probably not over 5 per cent at most would be considered serious enough to warrant consideration of therapy. Present concepts are that therapy be recommended only in patients with acute pulmonary histoplasmosis who are dangerously ill or whose lesions, if not treated would, by their location, cause them later complications.

Amphotericin has been used occasionally in severe cases of acute pulmonary histoplasmosis, particularly those with severe toxicity, prolonged illness and high fever. Rubin et al.³⁹ reported such therapy with satisfactory results. A total of 16 days of intravenous therapy with 50 mg. per day was given to this patient. Yates et al.,⁵⁹ Baum and Schwarz,⁴ Harrell and Bocobo²¹ and others have reported satisfactory results in the treatment of the acute disease with amphotericin.

Schwartz⁴³ has suggested that at least some of the toxic manifestations may be due to allergy and that the use of cortisone covered by amphotericin might be indicated. Packard et al.³⁶ in several cases used cortisone without amphotericin for the toxemia, but after the immune response had been built up. Under ordinary circumstances, however, corticosteroids are contraindicated at any stage of the disease, as they are in tuberculosis, unless covered by specific therapy.

Certain types of disease such as intense hilar or mediastinal involvement or failure of nodes in these areas to regress promptly should also be seriously considered for amphotericin therapy. Here prevention of atelectasis and later bronchiectasis and mediastinal fibrosis are prime considerations. If given to combat the presence of large mediastinal nodes causing atelectasis the drug would be continued until the nodes have diminished in size sufficiently to permit re-aeration of the lung. In any event the amount of therapy is varied with the patient and is usually much less than in the chronic type of disease.

Nodular disease which has relapsed and progressed as reported by Smith and Matthews⁴⁵ would also be considered for therapy.

Disseminated Histoplasmosis

This term is applied to the clinical manifestations of extrapulmonary spread of the fungus. It appears that a few organisms not infrequently become blood-borne from the lungs and lymph nodes during the acute stages of the disease. This transient fungemia appears of no clinical importance beyond causing a few splenic calcifications. However, in certain persons, possibly those with defective immune mechanisms, definite foci of disease are established in other than the pulmonary tissues. These may be evidenced clinically as an acute septicemic type usually in younger persons, as a *Histoplasma* meningitis or, in older persons, as a chronic granulomatous type with adrenal involvement, accompanied by ulceration of the mucous membranes.

The severity of the untreated acute disseminated disease was earlier demonstrated by Bunnell and Furecolow⁸ and Christie et al.¹¹ This has perhaps best been documented by the Communicable Disease Center Cooperative Mycoses Study,¹³ in which it was established that the disease was fatal in 20 of 24 untreated cases observed by the group.

Amphotericin B appears to be the most satisfactory drug for the treatment of this type of histoplasmosis. In July 1959, Little et al.²⁶ reported the first satisfactory results of treatment of acute disseminated histoplasmosis in four infants from Louisville, Kentucky. Heyn and Giannoni²² reported successful treatment of two cases from Iowa. Utz and Treger⁵⁵ reported satisfactory results in four of seven cases. Two patients died and one was still on therapy in December 1959. Later Yates et al.⁵⁹ reported satisfactory results in an additional two cases of disseminated disease. Harrell and Bocobo²¹ in 1960 reported the treatment of 18 progressive disseminated cases, in nine of which improvement was dramatic. Seven of these showed clinical remission for periods up to 18 months. One patient died after initial improvement on oral therapy, and three other deaths occurred in patients who had been inadequately treated. Little, in 1962²⁷ reported satisfactory results in eight of nine cases, the one unsatisfactory result being in a child treated only three days. Satisfactory results in occasional single cases have also been reported.^{20, 38, 44}

The therapy of chronic disseminated histoplasmosis with amphotericin was first described by Lehan et al.,²⁴ who reported satisfactory results in two cases by the oral route and later good results in two of four cases treated intravenously.²⁵ Utz et al.⁵⁴ reported recovery in one of two patients treated intravenously.

A larger series of disseminated histoplasmosis is that reported by the Communicable Disease Center Cooperative Mycoses Study.¹³ Five deaths occurred among 22 patients treated with amphotericin, four of which were in 13 patients who did not receive adequate treatment. This series included both acute and chronic disseminated types.

Amphotericin B has also been employed in the treatment of some of the complications of dissemination as meningitis,^{35, 47} pericarditis^{19, 56} and endocarditis.^{15, 37}

Snyder and White⁴⁷ and Nelson et al.³⁵ reported recoveries in two cases of *Histoplasma* meningitis. One was in a five year old boy who developed a residual footdrop presumably associated with intrathecal therapy and the second a four month old infant who recovered from her infection but suffered permanent brain damage. She received no intrathecal treatment.

Gregoriades et al.¹⁹ and Webb and Herring⁵⁶ reported apparent cures of one case each of *Histoplasma* pericarditis with effusion by treatment with surgical drainage and amphotericin.

In July, 1962, Derby et al.¹⁵ reported that they had successfully treated the first patient with *Histoplasma* endocarditis with 4.8 gm. of amphotericin. She was well 20 months after discharge from the hospital. Palmer et al.³⁷ reported failure in a case treated with 1.3 gm. of amphotericin. They recommended at least six months of therapy with amphotericin.

In summary, it appears that therapy is imperative in both types of disseminated disease since most children with the acute type will die and all adults with the chronic type will eventually succumb to the disease. In the acute type in children early diagnosis and prompt therapy are more important than long duration of therapy. In adults, it appears that larger amounts of amphotericin (3 gm. or over) are indicated for longer periods to prevent relapse. Prompt diagnosis and amphotericin therapy seem to offer the only hope in the complications of dissemination involving the central nervous system and the heart. Again adequate dosage must be given.

Chronic Pulmonary Histoplasmosis

Chronic pulmonary histoplasmosis with its resemblance to chronic pulmonary tuberculosis has become a disease of increasing importance. Although the first cases were reported in 1948 by Bunnell and Furcolow⁸ and Johnson and Batson,²³ and only 11 cases could be found by Sutliff et al.⁵¹ in 1953, Furcolow and Brasher¹⁸ by 1956 were able to report 13 cases in one sanatorium, and to estimate that large numbers existed in the sanatoria of the United States.

Table 3 gives a resume of the literature of the treatment of chronic pulmonary histoplasmosis with amphotericin, exclusive of the two large

Table 3. Summary of Results of Amphotericin B Therapy in Chronic Histoplasmosis as Obtained from the Literature.

	APPARENT			NO CHANGE	DEAD FROM OTHER CAUSES	DEAD FROM HISTO- PLASMOSES
	TOTAL	RECOVERY	IMPROVED			
Beard et al. ⁶	1				1	
Harrell and Bocobo ²¹	9	1	7		1	
Seabury, 1961 ⁴⁴	10	8		2		
Smith and Matthews ⁴⁵	4	3				1
Baum and Schwarz ⁵	11		7	1		
Utz et al. ⁵⁴	1				1	2
Yates et al. ⁵⁹	27		15	6	4	2
Saliba ⁴⁰	4		4			
TOTAL	67	12	33	9	7	4
						2

cooperative group trials reported in detail below. A total of 67 patients have been treated, of which six have died, two of histoplasmosis and four of other causes. Forty-five of 67, or 67 per cent, have shown improvement or recovery. Nine patients have relapsed and seven were unchanged by therapy.

A large amount of data on the treatment of chronic pulmonary histoplasmosis with amphotericin has been collected by two cooperative studies. In the Veterans Administration Study,⁴⁸ improvement was noted in 13 of 17 treated cases and no change in four. Relapse occurred in four of their 17 cases, but all of these patients had received a total dose of less than 1 gm. of amphotericin.

The problem of treatment of chronic pulmonary histoplasmosis has been further defined by the Communicable Disease Center Cooperative

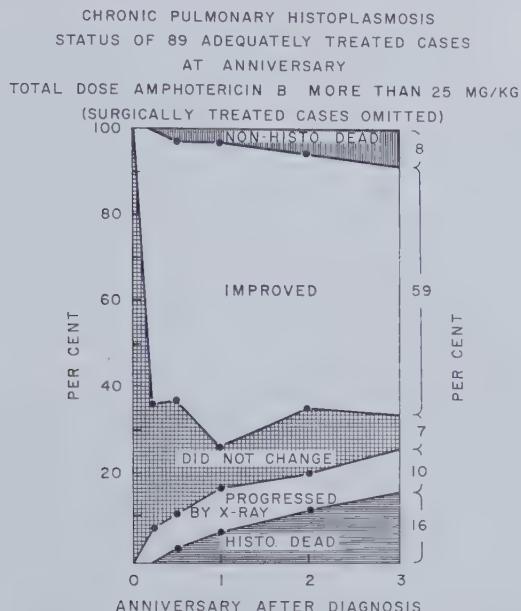


Fig. 1. (From J.A.M.A. 183: March 9, 1963.)

Mycoses Study of the Public Health Service,¹³ which has reported on the treatment with amphotericin of 172 cases of chronic pulmonary histoplasmosis. The critical factors affecting the results appeared to be the amount of drug the patient received and the period of observation of the patients following therapy. From these studies it appeared that small amounts of amphotericin (less than 25 mg./kg. body weight) had relatively little effect when compared with untreated cases. There did appear to be some transient early effect in decreasing progression and death from the disease. However, when larger doses were given, or more than 25 mg./kg., as shown in Figure 1, the prognosis was markedly improved over the untreated cases. The mortality was decreased and almost 60 per cent showed improvement over a three year follow-up period.

In summary, it appears that amphotericin has a definite place in the therapy of acute pulmonary histoplasmosis and should probably be more widely employed as a preventive for the later complications of acute pulmonary histoplasmosis. It appears to be life-saving in acute and chronic disseminated histoplasmosis, and to be effective in lowering mortality and decreasing progression of the disease in the chronic pulmonary type. Since amphotericin B is the only effective antifungal agent now commercially available for the systemic mycoses,* it appears desirable that its use be extended and more thoroughly understood.

* Because it is not now commercially available or in production this paper will include no references to antifungal antibiotic X5079C, which has been reported on by Utz et al.⁵³ and others.^{16, 50}

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Coccidioidomycosis and Amphotericin B

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THE ENDEMIC AREA for coccidioidomycosis has been geographically defined,^{42, 45, 46} and is apparently conterminous with the lower Sonoran life zone.²¹ Distribution of the pathogenic fungus *Coccidioides immitis* within this area is not uniform, but "spotty" in character. The southern San Joaquin Valley in California and the Phoenix-Tucson area of Arizona are similar in that they possess the most marked soil contamination by the fungus and in these areas a maximal infection rate of 25 per cent of newly arrived nonimmune persons is possible.³¹ The degree of soil contamination by *C. immitis* is also reflected by the incidence of coccidioidal infection among cattle, which provides a natural index for the degree of endemicity in any area.²²

PATHOGENESIS AND DIAGNOSIS

The present concept of the natural course of coccidioidomycosis began 25 years ago with the classic studies of Gifford,¹² Dickson^{6, 7} and Smith.²⁹ In the past ten years, approximately 600 contributions have appeared in the scientific literature,⁴ bringing additional refinement to present knowledge. With the beginning of our own studies of coccidioidal disease in the San Joaquin Valley, first reported from Springville in 1941,⁴¹ the need was felt for a systemization of the disease based upon the roentgenographic pulmonary changes. The hope that this could be correlated with its pathogenesis was a desirable but somewhat unsophisticated wish. So variable are its manifestations that Mackler in 1951 has described coccidioidomycosis as "a disease without a natural history."²⁰ The multiple aspects of the disease process brought realization, as observations continued, that coccidioidomycosis possessed a bizarreness that defied classification. The experience derived from almost daily encounters with its pathologic manifestations during the past 20 years has made possible some systemization which lends definite usefulness in the medical and surgical management of the patient with coccidioidomycosis (Table 1).

The initial infection, produced by entry of the highly infectious chlamydospore of *C. immitis* into the respiratory tract, occurs usually via spore-laden dust and produces only mild illness in two-thirds of patients.

Table 1. Coccidioidomycosis: A System of Classification**I. PRIMARY COCCIDIOMYCOSES**

- A. The primary pulmonary lesion (roentgenographic)
 - 1. Pneumonitis (2-6 weeks' duration)
 - 2. Infiltration (over 6 weeks' duration)
 - 3. Consolidation
 - 4. Lymphadenitis, hilar
 - 5. Cavitation, transient
 - 6. Nodular densities, single or multiple
 - 7. Pleural effusion
 - 8. Mixed lesions, protean
- B. Residual pulmonary lesion (roentgenographic)
 - 1. Coccidioidoma (solid, round focus) { nearby satellite densities often present
 - 2. Coccidioidal abscess (thick-walled) }
 - 3. Cavitation (cystlike, thin-walled)
 - 4. End point lesion (calcification, fibrosis, localized bronchiectasis)
- C. Extending pulmonary lesion (roentgenographic)

A local extension of any of the primary or residual lesions, but confined to the same body system without widespread dissemination.

 - 1. Infiltrate, progressive
 - 2. Coccidioidoma, enlarging
 - 3. Coccidioidoma, excavating
 - 4. Coccidioidoma, becoming multiple
 - 5. Cavitation, enlarging
 - 6. Cavitation, becoming multiple
 - 7. Cavitation, transpleural rupture
 - 8. Cavitation, recurrent

II. DISSEMINATING COCCIDIOMYCOSES (by systemic involvement)

Acute: Less than 6 months' duration. *Chronic:* More than 6 months' duration.

- A. Respiratory
 - 1. Laryngopharyngeal
 - 2. Tracheobronchial
 - 3. Lung
 - 4. Pleural
 - 5. Thoracic wall
 - E. Peripheral granuloma
 - F. Visceral and peritoneal
 - G. Urogenital
 - H. Cardiac
 - I. Eye
 - J. Meningeal
- B. Lymphatic
- C. Skeletal
- D. Cutaneous
 - 1. Of hematogenous origin
 - 2. By direct extension

III. PRIMARY EXTRAPULMONARY COCCIDIOMYCOSES

Infection by primary cutaneous inoculation, usually with secondary lymphadenopathy (chancreiform syndrome).

That coccidioidal infection has even occurred is in many such patients indicated only by the development of skin sensitivity to coccidioidin, and complete recovery of the patient from such subclinical illness is followed by lasting immunity. In the remaining third of the patient group undergoing primary infection, a more severe illness results following the usual incubation period of two to three weeks. This is accompanied by respiratory symptoms including fever, chills, cough, chest pain and increasing lassitude and weakness. In 25 per cent of female patients, but only 4 per cent of male patients, primary coccidioidomycosis will be accompanied by a skin rash (erythema nodosum or erythema multiforme). These skin manifestations are suggestive of coccidioidal infection, but if they are absent the medical history indicating recent exposure within the endemic area may be the only clinical lead toward correct recognition of the existence of primary coccidioidomycosis. A positive intracutaneous reaction to 0.1 cc. of a 1:100 dilution of coccidioidin, manifested by the appearance of induration 24 to 48 hours later, will also be suggestive. Such skin sensitivity will usually appear three to four weeks after the

initial pulmonary infection has occurred. Serial roentgenograms of the chest are necessary to follow adequately the inflammatory and infiltrative changes that usually appear within the lungs.

Serological evaluation is essential in the medical management of primary coccidioidomycosis. C. E. Smith has, by his important contributions, shown that such tests are successful in 92 per cent of patients in establishing the diagnosis and forecasting the prognosis.^{30, 33} The presence of precipitins in the serum indicates the recentness of the infection, whereas the titer of complement fixation is more closely correlated with its severity. Complement fixation appearing in serum dilutions as high as 1:64, and, with continuing elevation of titer, is indicative of impending dissemination of the invading fungus from its primary focus in the lung. With such failure of focalization of the initial infection, the patient's recovery is seriously threatened since a 50 per cent mortality is associated with disseminated coccidioidomycosis. Fortunately, this is uncommon, occurring in not more than 0.5 per cent of patients, more frequently in the male. Racial susceptibility plays an important role and dissemination occurs at least twenty times as frequently in the Filipino and Negro as in the Caucasian. An exception is coccidioidal meningitis, which occurs more often in white-skinned patients.

TREATMENT

Adequate medical management of coccidioidal disease is based upon an understanding of these pathogenic manifestations (Table 1). This applies equally to medical or surgical methods of control. Completely effective therapy would involve:

1. The control of severe primary coccidioidomycosis.
2. The prevention of dissemination, or its arrest if it has occurred.
3. The prevention of the development of residual pulmonary lesions (cavitation, solid densities [coccidioidoma], chronic abscesses).
4. The control of locally extending pulmonary lesions of chronic type.
5. In prevention:
 - a. Adequate surgical coverage, to protect against the occasional severe postoperative complications related to pulmonary resections.
 - b. Effective coverage against systemic spread of the infection during the removal or drainage of peripheral granulomatous lesions; i.e., abscesses, sinus tracts, necrotic lymph nodes and infected bone.
 - c. Coverage for the patient with active coccidioidal disease who is receiving corticosteroid therapy.
 - d. Protection of the pregnant patient who contracts primary coccidioidal disease.
 - e. Control of extending or progressive coccidioidal disease in the diabetic patient.

The discovery of amphotericin B,* reported in 1956 by Gold¹³ and

* Amphotericin B was used as the preparation Fungizone prepared by E. R. Squibb & Sons.

Vandeputte, et al.³⁹ provided for the first time a means toward effective therapy as outlined above.

Amphotericin B is a yellow powder which is only slightly soluble in water. It is derived from *Streptomyces nodosus*, which was found in a soil specimen from the Orinoco River Valley of Venezuela. Its effectiveness against *C. immitis* in animals was described by Sternberg,³⁵ Steinberg,³⁴ and Halde.¹⁵ Its use in patients was described by Littmann,^{18, 19} Seabury,²⁸ Colwell,⁵ Utz,³⁸ Newcomer,²³ Klapper,¹⁶ Winn,⁴³ Smith³² and Einstein.⁸ Its intravenous use requires dispersion with sodium deoxycholate in almost equal proportion. Since its discovery, it has continued to grow in stature as the first important antibiotic effective against not only *C. immitis*, but also other pathogenic fungi which produce deep mycotic disease. Coccidioidal infection is more resistant and less responsive to the antifungal effect of amphotericin B than the other pathogenic fungi and more intensive and prolonged therapy is required for its control.

Primary Coccidioidomycosis

The troublesome side reactions and inherent toxicity of intravenously administered amphotericin B have caused it to be withheld except in severe coccidioidal infections. With experience, however, there is a growing conviction that it should not always be so withheld but given in minimal total dosage of not more than 1.0 gm. for earlier control of severe primary coccidioidomycosis. If the patient is under one year of age and a member of a susceptible race, such early but minimal use of amphotericin B will deserve careful consideration. If the chest roentgenogram reveals extensive or persistent pulmonary involvement, with associated hilar and paratracheal lymphadenopathy, such treatment is indicated. Primary coccidioidomycosis occurring during pregnancy or in a diabetic would also merit amphotericin B therapy. It is conceivable that earlier treatment might prevent the development of some of the chronic pulmonary sequelae that follow primary pulmonary infection. As used in the treatment of primary coccidioidomycosis, however, intravenous administration of amphotericin B has failed in several instances in the prevention of coccidioidal meningitis, which has appeared after such treatment was stopped.

Serial chest roentgenograms are useful in estimating the severity of the infection producing the pulmonary changes of primary disease, and also the degree of activity of the infection in chronic residual lesions left by the initial pulmonary infection. Therefore, chest roentgenograms should be made every three months for at least a year after recovery. Serological tests, carried out at monthly intervals, are also necessary in the evaluation of activity of the infection.

Pulmonary lesions of residual type appear in about 5 per cent of patients recovering from primary coccidioidomycosis, and are listed in Table 1, IB. These include cavitation, solid densities and chronic localized abscesses. They are ordinarily not associated with a very high level of activity of the infection, and only occasionally does progressive disease result from such lesions. Any change in their roentgenographic appearance, as outlined under IC in the table, is important, but must be differentiated from actual dissemination.⁴⁴ A rise or fall of the titer of

complement fixation provides an important guide in this respect. Such local activity, indicated by the waxing and waning of the roentgenographic appearance of these pulmonary sequelae, may be controlled by short periods of intravenous amphotericin B therapy. Surgical excision may become necessary for elimination of an excavating coccidioidoma or a chronic coccidioidal abscess in the lung. Persisting or enlarging cavitary lesions are also true surgical problems.

Disseminating Coccidioidomycosis

Disseminating coccidioidomycosis (Table I, II) is identified and defined by the associated systemic involvement and the accompanying serological change (a rising complement fixation titer of 1:64 or more). Detailed description of the multisystemic and granulomatous changes produced by dissemination have been presented in the literature.^{10, 11} Disseminating coccidioidomycosis can be of acute or chronic duration, and the effectiveness of amphotericin B in its arrest and the healing of many types of peripheral lesions and systemic involvement has been proved. With such treatment, the concomitant use of indicated and definitive surgical treatment, such as the drainage of abscesses, resection of sinuses, removal of infected bone and cauterization of verrucous or ulcerating skin lesions, is required.

Case 80, Table 3, is illustrative. A 42 year old male Negro recovered from severe multisystemic dissemination after 41 weeks of intravenous administration of amphotericin B, and a total dosage of 11,480 mg. On admission this patient was markedly toxic, febrile, and unable to swallow due to a retropharyngeal coccidioidal abscess. Improvement began soon after initiation of intravenous amphotericin B therapy and partial surgical drainage of the abscess. Resection of the wing of the right ilium was performed 3 weeks after admission because of an osteolytic coccidioidal lesion of the bone. Clearing of a miliary pulmonary infiltrate followed, and there was healing of a verrucous skin lesion and regression of cervical lymphadenopathy. Examination of the lumbar fluid on admission had also disclosed a complement fixation titer of 4+ in a 1:16 dilution, and elevation of serum protein to 320 mg./100 ml. There was very little cytological response however, and the quantitative sugar did not recede from a level of 68 to 98 mg./100 ml. Complement fixation remained positive for over 2 months on 4 occasions, and then became negative. These findings, indicating possible coccidioidal meningitis, were reversed completely at the end of the sixth month after beginning intravenous amphotericin B. Roentgenograms made several months later also demonstrated healing of a destructive osteitis involving the bodies of the second and third lumbar vertebrae. Because of the severity of the dissemination, planned interval therapy (460 mg. of amphotericin B) was given intravenously 7 months after completion of the first course of treatment, again 15 months later (840 mg.), and 25 months afterward (705 mg.). The patient remains well 32 months after the initial treatment period and all areas of previous involvement remain healed. There has been moderate loss of renal function, but he has resumed his previous occupation as an agricultural worker and the serum complement fixation titer has receded from a high value of 1:512 to a 1:32 serum dilution.

Coccidioidal Meningitis

Coccidioidal meningitis, notoriously insidious in onset, usually occurs

as a single manifestation of dissemination from the initial pulmonary focus. Combined intravenous and intrathecal amphotericin B will be required in order to preserve life because, if the meningitis is untreated, the mortality approaches 100 per cent within one year after the onset.⁸ A total intravenous dosage of not more than 5 gm. of amphotericin B is desirable, and treatment can then be continued with suppressive intrathecal administration (via the cisterna magna) in place of such intravenous therapy, and in order to minimize the nephrotoxic effect of amphotericin B. The intrathecal administration of amphotericin B can be carried out via the lumbar canal or the cisterna magna. The latter is preferred because it is closer to the base of the brain, which is the chief site of coccidioidal involvement of the meninges. This approach also avoids the subacute arachnoiditis (Froin syndrome) that frequently complicates continued injection of amphotericin B into the lumbar sac.

The intensive treatment of coccidioidal meningitis requires a hospital regimen of combined intravenous and intrathecal amphotericin B therapy. Injections via the lumbar canal of not over 0.5 mg. can be given twice weekly, and alternating cisternal injections of the same dosage also given twice weekly. Such a regimen would call for intrathecal administration on four days of each week. Freshly made dilutions, using sterile distilled water, without preservative, and a concentration of 0.25 mg. of amphotericin B per cc., are used in all intrathecal administration. The starting dose is 0.1 cc. of the above dilution and this is gradually increased until 0.5 mg. (2 cc. of solution) can be given without excessive discomfort. This minimal starting amount is important and the dosage is increased slowly until 0.5 mg. is reached. Beginning the injections in the lumbar canal also seems to increase drug tolerance in the cisternal area, and the first several injections are given at two or three day intervals via the lumbar sac alone, before starting the cisternal injections. These are also begun with the same starting dosage of 0.1 cc. At each injection the solution is diluted in the syringe with two or three times the volume of cerebrospinal fluid. There is recent evidence that diluting the lumbar injection with six to eight times the volume of spinal fluid results in better distribution of the antifungal agent.²⁵ As a part of the autopsy findings on patient No. 57, who had received a total of 202 lumbar canal injections of amphotericin B and 83 injections into the cisterna magna, there was very little gross evidence of local change involving the meninges in the cisternal area. Apparently the subarachnoid space, defined as the cisterna magna, tolerates such local therapy without any permanent changes related to local or chemical irritation. This may be partly due to the low and diluted dosage of 0.5 mg. as administered. Cisternal injections are always followed by headache of variable severity. Sedation, including codeine, should be given before the procedure. If arachnoiditis appears in the lumbar area, then only cisternal injections are given twice weekly, and these can later be decreased to five day intervals. This regimen of intrathecal therapy is designed to secure reversion of complement fixation within the spinal fluid, or to prevent its appearance in the patient who was negative from the first. When such serological reversion has occurred and there is a return of the quantitative protein, glucose and cell count values toward normal, the patient can be discharged to an

outpatient regimen of sustained suppressive cisternal therapy. This is necessary because of the tendency of coccidioidal meningitis to relapse, and consists of the weekly administration of 0.5 mg. of amphotericin B into the cisterna magna. Such treatment is compatible with ordinary occupational or school routines. This outpatient regimen should be maintained for at least three months and, if reversion of complement fixation has not occurred, continued until it takes place. Because amphotericin B is only fungistatic in action against *C. immitis*, it is possible that this type of suppression of *C. immitis* permits development of sufficient immune response by the host to accomplish actual healing.

Primary extrapulmonary infection produced by *C. immitis* is unusual (Table 1, III), and is ordinarily followed by recovery.⁴⁰ A short period of intravenous amphotericin B may become necessary along with local treatment of the primary cutaneous area of ulceration, using 3 per cent amphotericin B lotion or ointment.

Summary of Indications for Intravenous and Intrathecal Amphotericin B

The indications for intravenous amphotericin B are summarized in Table 2. It must be emphasized in referring to this table that no single clinical or laboratory finding can itself be an indicator for such therapy without consideration of the other factors listed. Each may modify the decision and make it either a matter of urgency, as in impending or full-blown dissemination, or a rather routine procedure in the prophylactic control of acute primary coccidioidal pneumonitis. An overall concept of the problem is required in each instance before committing the patient to a course of intravenous amphotericin B, and especially

Table 2. Indications for Intravenous Therapy with Amphotericin B in Coccidioidal Disease

-
1. Severe primary coccidioidomycosis with persistent *fever, prostration, extending or persisting pulmonary involvement, hilar or mediastinal adenopathy, elevated erythrocyte sedimentation rate, leukocytosis over 15,000 and eosinophilia over 15 per cent.*
 2. Unstable serology, manifested by:
 - (a) *Rising titer of complement fixation* (above 1:64 dilution).
 - (b) *Persisting precipitins.*
 - (c) *Incomplete complement fixation.*
 3. *Evidence of spread* of the infectious agent from the primary pulmonary focus to other systems, such as lymphatic, cutaneous, skeletal, pleuroperitoneal, cardiac, genitourinary or meningeal.
 4. A weak or negative skin reaction to coccidioidin (1:10 dilution).
 5. *Racial susceptibility:* Negro, Filipino.
 6. For surgical coverage, given 2 to 3 weeks before operation as in removal of large pulmonary cavities, destroyed areas of lung, ruptured cavities with threatened empyema, other excisional or drainage procedures, i.e., removal of infected bone, gonads, lymph nodes, sinus tracts, drainage of abscesses.
 7. For prophylactic coverage when primary coccidioidomycosis occurs during pregnancy or when active coccidioidal disease occurs in the diabetic. During *administration of corticosteroids.*
-

Italics in above indicates more important criteria.

before setting the total dosage. The factors itemized in Table 2 are the guideposts, any combination of which will, by proper interpretation, indicate the need for such specific antifungal therapy. For example, the persistence of serum precipitins alone, or the existence of a primary coccidioidal infection in a Negro or Filipino, would not in themselves be sufficient indication. But, given a Negro patient with primary coccidioidomycosis who is obviously toxic and ill and with a titer of complement fixation already at a 1:64 serum dilution, early intravenous amphotericin B would clearly seem to be needed. A maximal dosage of 5 gm. should not ordinarily be exceeded unless the infection is severe or has disseminated. The administration of over 10 gm. will gravely increase the likelihood of irreversible and toxic renal changes. The necessity to preserve life, however, would justify committing the patient to some loss of renal function.

Our observations made with amphotericin B began in 1956 and were reported in 1959.⁴³ The effectiveness of this fungistatic agent against coccidioidal disease was reported at that time. Later studies have continued to support these findings, and that the antifungal agent is effective against *C. immitis* when given either intravenously or intrathecally. It became apparent from the first that the treatment was not a simple procedure and some contriving was necessary to accomplish intravenous and intrathecal administration successfully. It was mandatory to minimize the accompanying side reactions in order to gain patient acceptance for the relatively long therapeutic period necessary for the control of severe coccidioidal disease. The recognition of the toxic manifestations that follow intravenous therapy became important and has required some moderation in the total dose administered. Our experience to date is aptly described by Wilson, who states, "Amphotericin B is more valuable than any drug previously tested extensively, although it is undesirably but not impractically toxic."⁴⁰

Toxic Reactions to Amphotericin B

The usual side reactions of chilling, febrile changes, nausea, vomiting and headache are most marked during the initial treatment period and become less in intensity as therapy proceeds. They are somewhat controllable by the slow administration of a gradually increasing increment of well-diluted amphotericin B (using 100 to 150 cc. of 5 per cent glucose in water per 10 mg. of amphotericin B). This is important, especially during the first two weeks and until reaching an average dose of 1 mg. per kg. body weight. Children have less side reactions and tolerate somewhat higher dosage, but not exceeding 1.5 mg. per kg. The "cut-off" technique of intravenous administration is very useful, especially in the minimizing of severe chills and phlebitis (Fig. 1).

Also effective in partial control of the side reactions has been the administration of hydrocortisone succinate, using a dosage up to 60 mg. for the average adult. In our experience 30 to 40 mg. has seemed sufficient in most instances. This can be given by intramuscular injection two hours before intravenous administration, or included with the amphotericin B solution (Bottle A, Fig. 1). In one patient critically ill with acutely disseminating coccidioidomycosis, recovery followed a total

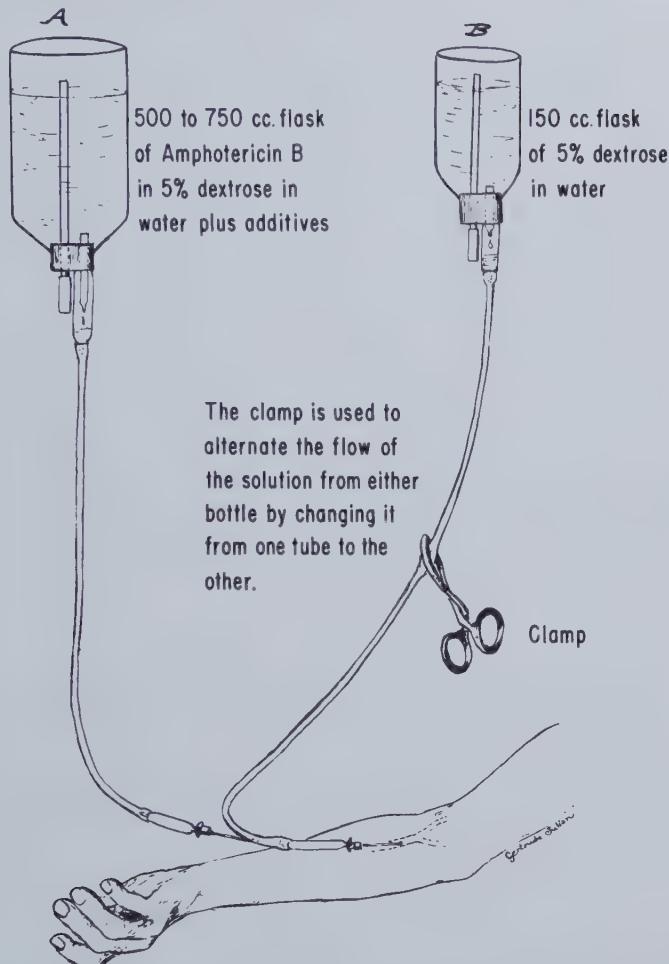


Fig. 1. A method for the control of phlebitis and side effects during intravenous administration of amphotericin B. A small needle (gauge 22 or 23) is used and introduced into a peripheral vein with a 2 cc. syringe (a special scalp vein set-up, available from Cutter Laboratories, Berkeley, California, is used in small children). This is connected to bottle B containing 150 cc. of 5 per cent dextrose in water. Bottle A, containing usually 500 to 800 cc. of 5 per cent dextrose in water, plus the desired dose of amphotericin B, is connected by a 20 or 21 gauge needle into the terminal portion of the bottle B tubing. The following additive may be included in this solution of amphotericin B in bottle A: Heparin sodium, 10 to 20 mg. Chills during and following the intravenous administration of amphotericin B are minimized by: (1) Extra blanket (electric) or hot water bottles. (2) By 15 minute "cut-off" technique. Clamp is changed by the nurse from bottle A tubing to bottle B tubing every 15 minutes for a period of 2 to 3 minutes. Shaking bottle A during the cut-off period prevents any tendency for the solubilized suspension to settle into the neck of the bottle and produce undesirable concentration. This procedure also minimizes phlebitis by washing out the vein periodically. If a chill develops, this method permits continuation of intravenous administration, giving only bottle B (5 per cent dextrose in water) slowly, until the chill subsides, and then restarting amphotericin B by changing the clamp. Premedication, usually necessary in the early course of intravenous treatment and given 30 minutes beforehand, may include 5 to 10 gr. acetylsalicylic acid (repeated in 2 hours) and/or 25 to 50 mg. of diphenhydramine hydrochloride (Benadryl).

intravenous dosage of 7781 mg. of amphotericin B, plus hydrocortisone succinate given daily in a dosage of 100 to 300 mg. and over a period of three months. Despite the severity of her illness, this patient remained relatively free of distressing side reactions during the period of intensive intravenous therapy. A period of considerable discomfort followed withdrawal of the corticosteroid until the depressed adrenal function returned to normal. Saliba,²⁶ who used intravenous amphotericin B in 22 patients, also reports great improvement in the control of toxic reactions by the use of 20 mg. of hydrocortisone daily. Tynes et al.³⁷ have recently reported a reduction of 22 per cent in the objective side reactions produced in patients under amphotericin B therapy by the concomitant use of hydrocortisone. They did note that there was striking variation, however, from one patient to another. Most notable was reduction in the frequency of fever, chills and nausea. Their observations were limited to a group of 22 patients, who received 112 to 160 treatments in different phases. Only one of their patients had coccidioidal disease. Recent studies¹⁴ suggest that purification of amphotericin B may reduce the severity of side reactions. A particular lot of amphotericin B in which the impurities were reduced to 8 per cent, and no amphotericin A was present, produced less severe side reactions and less local chemical irritation on intrathecal administration.

The three chief toxic manifestations following intravenous therapy include:

1. *Lowering of hemoglobin and red cell values*, which varies among patients. In part this may be due to interference with the transferrin system. Transfusions are required for correction.

2. *Hypokalemia*, which is not uncommon, and requires correction by the intravenous or oral administration of potassium during the therapeutic period.

3. *Nephrotoxicity* which is of greater importance than either of the above. In 1962 Sanford and his associates²⁷ stated that in three renal biopsy studies marked pathologic changes were demonstrated, including nephrocalcinosis, in the kidneys of patients treated with amphotericin B. Inulin clearance tests and renal plasma flow studies were confirmatory of related functional loss. In 1960, Beard and his associates² reported that "Amphotericin B has a definite suppressive effect on normal renal physiology." They believed that this was only temporary and cleared rapidly following completion of therapy. Also in 1960, Rhoades²⁴ showed that there was significant lowering of inulin and para-aminohippurate clearance values. He felt that in three renal biopsy studies histologic findings were consistent with the observed alterations in renal function, and concluded that, although permanent renal damage due to amphotericin B could not be shown, recovery after amphotericin B was discontinued was not as prompt or complete as previously believed.

In a study of 100 patients who received intravenous amphotericin B (Table 3), there appears to be a relationship between the degree of nephrotoxicity and the total amount of amphotericin B administered. It is probable that amphotericin B, due to its insoluble nature, is retained in certain body tissues over long periods. The greater the dosage, the

longer the duration of the toxic effect. In our earlier observations it was felt that blood urea nitrogen determinations were sufficient in measuring the degree of renal impairment that was occurring. It was learned later that false reassurance was given by these values, especially when they subsided after the usual rise during the initial period of treatment. It has become apparent that a much more reliable criterion for estimating the nephrotoxic effect is available in the measurement of serum creatinine clearance per minute.³⁶ Such conclusions are supported by study of the data derived from the 100 patients who received various doses of the fungistatic agent. The depression of creatinine serum clearance occurring during treatment, and its slow return toward normal values following cessation of amphotericin B, is indicative of the retention of the antibiotic, or its catabolic products, in the tissues. Continued depression of the clearances, and particularly falling values long after discontinuation of intravenous administration of large doses of amphotericin B, indicates serious and progressive loss of renal function. This is illustrated in Cases 57, 58 and 70 (Table 3). Of these three patients, No. 57 died of renal insufficiency 14½ months after receiving 14.275 gm. of amphotericin B. Patient No. 70 has continued to show progressive decrease of creatinine clearances nine months after treatment was stopped, which included a total dosage of 16.785 gm. Patient No. 58 is alive, after receiving 21.520 gm. of amphotericin B, because of a successful renal transplant done on December 12, 1962 by Drs. Joseph E. Murray, J. Hartwell Harrison and John P. Merrill at the Peter Bent Brigham Hospital in Boston. The renal lesions observed in two patients (No. 57 and No. 58) resemble one another and consist of epithelial cell proliferation and increased density of the glomerular tuft, focal atrophy and calcification of the distal portion of the nephron, and interstitial edema and fibrosis. Irreversible alterations, in the pattern described, occur with little or no reduction in the size of the kidneys. These findings are described in more detail by Reynolds, Tomkiewicz and Dammin on page 1149 of this publication.

Oral Therapy with Amphotericin B

Oral amphotericin B has limited use in the treatment of coccidioidomycosis. Absorption from the gastrointestinal tract is so little that demonstrable levels in the blood serum do not ordinarily follow. Baum and Schwartz¹ reported on the use of as much as 4 gm. of amphotericin B daily by mouth without detectable blood levels. These workers used the relatively insoluble 200 mg. amphotericin B tablets. Campbell and Hill³ and Kravetz et al.¹⁷ reported unsuccessful attempts to use amphotericin B by stomach tube instillation in 9 patients. Only low blood serum levels were obtained and the results were variable due to the marked systemic reactions of diarrhea, vomiting and nausea that interfered with this method of administration. Groel¹⁴ states that, despite poor and inconsistent absorption of amphotericin B from the intestinal tract, definite therapeutic responses have been obtained in several cases of North American blastomycosis, which have primarily cutaneous lesions. These have shown response despite the apparent absence of a significant blood level. In 1957, Fiese⁹ described improvement in a patient with extensive coccidioidal granuloma of the face following the daily use of 2.4 gm. of oral amphotericin B for a total dosage of 200 gm. There was accompanying regression of the titer of serum complement fixation.

Table 3. A Group of 100 Patients Treated with Amphotericin B Showing Total Dosage, Renal Effects and Clinical Results.

CASE NO.	PATIENT	AGE	SEX	RACE	INDICATION FOR INTRAVENOUS AMPHOTERICIN B THERAPY (Footnote 1)	COMPLETION DATE OF IV AMPHOTERICIN B THERAPY	INTERVAL SINCE INTRAVENOUS AMPHOTERICIN B THERAPY	DOSE OF AMPHOTERICIN B (in mg.)	LOSS OF RENAL FUNCTION (Footnote 2)		RESULT OF TREATMENT	
									V-1	IV-2	IV-3	IV-3
1	P.G.	48	M	Filip.			4/2/57	287	A	B	Recovered	
2	L.C.	76	M	Cauc.			7/14/57	3102	Dead (1)*	B	Dead (1)*	
3	L.H.	30	F	Cauc.			7/17/57	3100	Recovered	A	Recovered	
4	A.S.	2	M	Negro			9/20/57	642	"	A	"	
5	V.E.	55	M	Filip.			10/13/57	710	"	A	"	
6	V.R.	35	F	Cauc.			12/6/57	190	"	A	"	
7	P.C.	5	M	Cauc.			3/25/58	737	"	A	"	
8	C.F.	55	M	Cauc.			4/9/58	1420	"	A	"	
9	P.T.	14	M	Cauc.			5/5/58	1691	Dead (2)*	B	Dead (2)*	
10	W.L.	69	M	Negro			7/31/58	3255	Arrested	A	Arrested	
11	B.D.	28	M	Cauc.			8/2/58	2872	"	B	Recovered	
12	A.S.	2	M	Negro			9/27/58	1690	"	A	"	
13	G.B.	44	F	Cauc.			11/6/58	1454	"	A	"	
14	R.M.	54	M	Cauc.			12/15/58	2787	"	A	"	
15	E.P.	10	M	Ind.			1/23/59	3078	"	A	"	
16	T.T.	54	M	Filip.			2/4/59	3320	"	A	"	
17	P.B.	61	M	Filip.			3/20/59	3210	"	A	"	
18	J.W.	33	M	Cauc.			3/27/59	10372	Dead (2)*	D	Recovered	
19	S.P.	4	F	Negro			4/14/59	1012	"	A	"	
20	E.M.	21	F	Cauc.			4/22/59	12220	"	A	"	
21	R.P.	2	M	Cauc.			7/31/59	1946	"	A	"	
22	B.N.	35	M	Mex.			8/25/59	670	"	A	"	
23	R.O.	55	F	Cauc.			8/29/59	3015	"	A	"	
24	E.S.	22	F	Cauc.			9/4/59	2672	"	A	"	
25	L.H.	52	M	Cauc.			10/14/59	1905	Improved	A	Recovered	
26	F.M.	47	M	Filip.			10/16/59	2600	Recovered	A	Recovered	
27	S.C.	49	M	Cauc.			10/23/59	3414	Dead (2)*	C	Dead (2)*	
28	E.L.	6	F	Negro			11/2/59	3795	Recovered	A	Recovered	
29	A.R.	49	F	Filip.			11/9/59	2605	"	A	"	
30	J.M.	40	F	Cauc.			11/18/59	570	"	A	"	
31	F.R.	46	F	Cauc.			11/8/60	6440	"	D	"	
32	E.V.	25	F	Mex.			12/24/60	2965	"	A	"	
33	J.B.	28	M	Cauc.			1/19/60	765	"	A	"	
34	E.H.	18	F	Cauc.			3/11/60	480	"	A	"	
35	N.R.	54	M	Cauc.			6/4/60	4075	"	A	"	
36	A.Y.	54	F	Cauc.			6/13/60	2110	Dead (3)*	A	Dead (3)*	
37	D.C.	13	M	Cauc.			6/29/60	1365	Recovered	A	Recovered	
38	M.K.	5	M	Cauc.			6/12/60	105	"	A	"	
39	J.O.	33	M	Cauc.			8/2/60	3085	"	A	"	
40	L.S.	15	M	Mex.			8/15/60	4055	"	A	"	
41	A.D.	61	M	Filip.			9/25/60	1460	"	A	"	
42	D.F.	13	M	Cauc.			9/30/60	1255	"	A	"	
43	A.W.	34	F	Cauc.			9/30/60	1085	Arrested	B	Recovered	
44	E.G.	52	F	Mex.			12/13/60	4210	Recovered	A	Recovered	
45	G.E.	29	M	Negro			2/25/61	4980	"	A	"	
46	A.E.	22	M	Cauc.			3/17/61	885	"	A	"	
47	I.R.	25	M	Mex.			3/19/61	1225	"	A	"	

Coccidioidomycosis and Amphotericin B

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* Cause of death: (1) Coronary occlusion (nonrelated). (2) Coccidioidal meningitis (autopsy proof). (3) Cardiac arrest during surgery (nonrelated). (4) Renal insufficiency—nephrotoxicity (amphotericin B).

Although renal insufficiency occurred due to amphotericin B, death was prevented by a successful renal transplant at the Peter Bent Brigham Hospital on 12/12/62 (donor kidney from mother of patient).

Table 3 (Footnote 1). Indications for Intravenous Amphotericin B
 (An explanation of the coding used in Table 3)

I. SEVERE PRIMARY COCCIDIOMYCOSIS

For example: Titer of complement fixation remaining at 1:64 or below, in a racially susceptible person, with a hazardous type of infection; i.e., *C. immitis* in pleural fluid

II. IMPENDING DISSEMINATION

For example: Titer of complement fixation at 1:64 or higher, in a racially susceptible person with severe illness

III. DISSEMINATING COCCIDIOMYCOSIS

1. Early (single peripheral or early systemic involvement)
2. Severe (multisystemic involvement)
3. Meningitis

IV. RESIDUAL PULMONARY DISEASE

1. Cavitation, solid densities, coccidioidoma, chronic abscesses
2. Extending pulmonary lesion

V. AMPHOTERICIN B COVERAGE

1. Surgical patient
 2. Pregnancy patient
 3. Other conditions; i.e., during corticosteroid therapy
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DISCUSSION

Data derived from the follow-up of the 100 recipients of intravenous amphotericin B is based upon the results of such treatment for active and serious types of coccidioidal disease. The effectiveness of amphotericin B is shown, and it retains its importance as the only available antifungal agent of proven value for the control of coccidioidal disease. In these 100 patients, there have been only three deaths related to the disease process and these were due to coccidioidal meningitis (Nos. 9, 18 and 27). A fourth death (No. 57) resulted from severe renal insufficiency which followed a high dosage of intravenous amphotericin B administration. Another patient (No. 58) also would have died from nephrotoxic changes, but is alive because of the successful renal transplant previously mentioned. Both patients (Nos. 57 and 58) had received large doses of intravenous amphotericin B for severe coccidioidal meningitis. A third patient (No. 70), who also received 16.75 gm. of amphotericin B for a chronic form of coccidioidal meningitis, has had no additional intravenous treatment for nine months. Because of decreasing serum creatinine clearances ($\text{Cer} = 22 \text{ ml./min.}$ on 3/8/63), he now has a definitely limited outlook. Our observations indicate that the earlier substitution of suppressive intrathecal injections of amphotericin B into the cisternal canal, in place of intravenous administration, might have arrested the coccidioidal meningitis in these three patients and lessened the total dosage of amphotericin B necessary and with less nephrotoxicity.

In Table 4, it will be noted that although the loss of renal function is predicated upon relatively simple types of laboratory criteria (see Footnote 2), that such patient grouping by the degree of toxicity manifested by loss of renal function, bears a definite relation to the total dose of intravenously administered amphotericin B. Those patients, comprising the majority of the group, who received less than 2 gm. have no detect-

Table 3 (Footnote 2). Criteria for Estimating Loss of Renal Function Based on Laboratory Findings and for Grouping of Patients
 (An explanation of the coding used in Table 3)

	A No loss	B Slight loss	C Moderate loss	D Moderate to severe loss	E Severe loss
Urine	Albumin—negative Occ. gran. casts Sp. gr. 1.002-1.030	Albumin—ft. trace Occ. coarse gran. casts Sp. gr. 1.002-1.020	Albumin—trace Coarse gran. casts Sp. gr. 1.010 or less	Albumin—1 to 2+ Many coarse gran. casts Sp. gr. approaching 1.010 fixed	Albumin—3 to 4+ Many casts, all types Sp. gr. 1.010 fixed
Blood urea nitrogen	10-18 mg./100 ml.	18-28 mg./100 ml.	30-50 mg./100 ml.	50-70 mg./100 ml.	Over 70 mg./100 ml.
Nonprotein nitrogen	25-35 mg./100 ml.	40 mg./100 ml. or less	60 mg./100 ml. or less	80 mg./100 ml. or less	Over 100 mg./100 ml.
Serum creatinine	0.6-1.2 mg./100 ml.	1.2-1.8 mg./100 ml.	1.8-2.4 mg./100 ml.	2.4-3.6 mg./100 ml.	3.6 mg./100 ml. or more
Creatinine clearance	M. 72-141 ml./min. F. 74-130 ml./min.	70-50 ml./min.	50-30 ml./min.	30-20 ml./min.	20 ml./min. or less

Table 4. A Group of 100 Patients Showing Relation Between Total Dosage of Amphotericin B and the Effects Upon Renal Function (As of March 1963)

TOTAL AMOUNT OF AMPHOTERICIN B ADMINISTERED INTRAVENOUSLY	FOLLOW-UP PERIOD AFTER TERMINATION OF INTRAVENOUS AMPHOTERICIN B THERAPY				
	3 to 6 months	6 to 12 months	12 to 24 months	24 to 48 months	Over 48 months
Under 1 gram	AAAAA B	AAA B	AAA	AAAA	AAAA
1 to 2 grams	AAA BB	AA B	AAAAAA BB	AAAAAAA	AAA B
2 to 5 grams	A B C D		AAAA AA B BB		AAAAAAA AAA B
5 to 10 grams	BBB C	AA BB	B	D	
10 to 20 grams	CC	B	DD	E	E
Over 20 grams					

See Table 3 (Footnote 2) for explanation of patient groups by laboratory criteria.

able, or slight loss of renal function. It is also doubtful that additional follow-up will show any increase of the loss of function that has occurred in those who have received less than 5 gm. (Exception: Patient No. 90, a 10 year old boy). It is probable that those patients who required a total intravenous dosage of 7 to 10 gm. will be left with permanent but partial loss of renal function. The outlook for the four living patients who received over 10 gm. is more guarded. In patient No. 18, who received 10.37 gm. and died of coccidioidal meningitis 3½ years ago, histologic proof of moderately severe renal damage was obtained.

SUMMARY

A concept of the pathogenesis of coccidioidomycosis is presented, and the diagnosis and treatment of the various stages of the disease process discussed. Amphotericin B remains the only antifungal agent available that is effective against *C. immitis*. One hundred patients who received amphotericin B for serious types of coccidioidal disease are reviewed. The generally favorable results of amphotericin B therapy are shown. The control of side reactions that accompany intravenous administration are described, including the use and effectiveness of hydrocortisone. The development of nephrotoxic changes is discussed in relation to the total dosage of amphotericin B administered intravenously. Better evaluation of such changes during therapy is obtained by serum creatinine clearance values than through blood urea nitrogen determinations. The long-term intravenous therapy used previously for coccidioidal meningitis can be

shortened by substitution of intrathecal therapy and with lessened nephrotoxic changes. The value of intrathecal therapy via the cisternal canal is described. More detailed data covering the diagnosis and treatment of coccidioidal meningitis will be presented in a forthcoming report.

Acknowledgment

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The Renal Lesion Related to Amphotericin B Treatment for Coccidioidomycosis

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RENAL TOXICITY associated with the administration of amphotericin B for treatment of systemic mycoses is characterized by hyposthenuria, uremia and decreased inulin and para-aminohippuric acid (PAH) clearances.^{1, 2, 8, 10, 14, 16, 18} These changes are associated with the deposition of calcium in renal tubules.^{4, 5, 12} Such toxic side effects are considered reversible when relatively small cumulative total doses (less than 7 gm.) of the antifungal agent are employed, since renal function tends toward normality upon cessation of therapy.^{1, 2, 10, 12, 18} Larger doses administered over longer periods may, however, result in irreversible renal insufficiency.^{14, 18}

The two cases presented here* are significant in that they demonstrate the distinctive pathological features of the renal lesion resulting from the administration of large total doses of amphotericin B.

* Patients S.L. and F.C. are Patients 57 and 58, respectively, in Dr. Winn's report¹⁸ which appears in this issue.

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Clinical Summaries

F.C. is a 23 year old man of Mexican lineage who developed pulmonary coccidioidomycosis in October, 1958, at which time treatment with amphotericin B was instituted. In January, 1959, meningeal involvement appeared. In the course of 3 years from the onset of his illness he received over 21 gm. of amphotericin B intravenously, and 171 mg. intrathecally. The last course of intravenous drug treatment ended in December, 1961, at which time the blood urea nitrogen was 39 mg. and the serum creatinine was 3.1 mg. per 100 ml. Without further drug therapy, the renal insufficiency progressed and in June, 1962, the blood urea nitrogen was 110 mg. and the serum creatinine 6.3 mg. per 100 ml. At this time, the patient was noted to be hypertensive. In November, 1962, upon admission to the Peter Bent Brigham Hospital, the blood urea nitrogen was 225 mg. and the creatinine 14.4 mg. per 100 ml. Serum antinuclear antibody was negative, and the antistreptolysin "O" titer less than 100 units. In December, 1962, the patient's right kidney was removed at the time of transplantation of a kidney from his mother. The left kidney was removed several weeks later. At the time of this writing, 5 months from the time of transplantation, the patient's clinical condition is good and the blood urea nitrogen is normal.⁷

S.L. This patient was a 20 year old man of Mexican lineage who developed pulmonary coccidioidomycosis in May, 1959. In July, 1959, he was found to have meningeal involvement. Initially there was a good response to intravenous and intrathecal amphotericin B. However, relapses occurred and repeated courses of therapy were required. By November, 1961, the patient had received over 14 gm. of amphotericin B intravenously and 162 mg. intrathecally. During the year following cessation of drug therapy, the serum creatinine rose from 2.8 mg. to 18 mg. per 100 ml. Hypertension was observed during this period and in February, 1963, the patient was noted to have a blood urea nitrogen of 228 mg. per 100 ml., was admitted to the hospital because of acute pulmonary edema, developed convulsions and died.

Pathological Findings

The kidneys of both patients were similar and showed but little reduction in size. Those of F.C. weighed 129 and 163 gm., and those of S.L. 170 and 180 gm. Their capsules were adherent and when stripped revealed finely granular, pale yellow-tan cortical surfaces. The cortex was slightly reduced in width and contained gray-white radial streaks. Green-brown deposits extending into the cortex were noted at the corticomedullary junction of the kidneys of F.C. (Fig. 1, 1) The cut surfaces of these kidneys were also unusually moist.

Microscopic examination of kidneys from both patients reveals an essentially identical lesion. Subcapsular glomeruli are small, fibrotic and hyalinized (Fig. 1, 2). Subjacent to this zone, the outer cortex appears compact with normal size glomeruli but tubules have reduced cross sectional areas. Glomeruli are enlarged, hypercellular and have thickened basement membranes in the vascular tuft in the juxtamedullary portion of the cortex (Fig. 1, 2, 3). Adhesions between visceral and parietal layers of Bowman's capsule are often noted in hypertrophic juxtamedullary glomeruli (Fig. 1, 3). (Hypertrophic glomerular changes are more pronounced in the kidneys of S.L.) Associated tubular components are lined by tall epithelium and have dilated lumens in this zone and in the medulla (Fig. 1, 2). Arcuate and interlobular arteries and afferent and efferent arterioles appear normal.

Calcium deposits are prominent within tubules and interstitial tissue in the cortex along the borders of the medullary rays (Fig. 1, 1, 2). These deposits, which are nonrefrangent, have the characteristic staining reactions of calcium phosphate,⁹ and may appear as fine granules within lumens of tubules containing remnants of epithelial cells (Fig. 1, 4). Adjacent tubules are completely replaced by irregularly round homogeneous deposits of calcium phosphate (Fig. 1, 4). Dense proteinaceous casts within tubular lumens and tubular basement membrane thickening are also prominent, particularly in the medullary rays. Increased loose, edematous interstitial tissues are noted in these areas.

Abundant yellow-brown ceroid pigment is present in the tubular epithelium of the cortex of the kidneys of patient F.C. Iron and lipid are found in other portions of the tubules in kidneys of both patients.

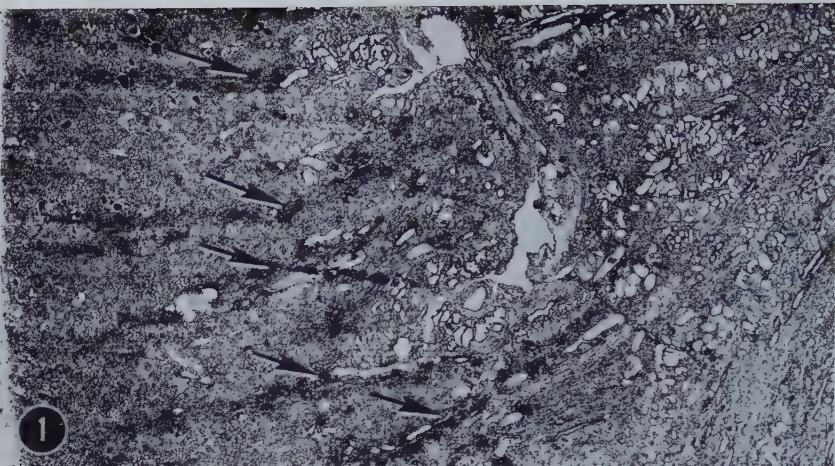
No localized accumulations of the patient's own globulins were found when frozen sections of the kidneys of patient F.C. were treated with fluorescein labeled anti-human globulin.

The continued presence of amphotericin B in the kidneys of patient F.C. was determined as follows: minced, fresh-frozen kidney was lyophilized and extracted several times with diethylether to remove the bulk of the lipids. The residue was then extracted two times with dimethylsulfoxide or methyl alcohol, and the absorption spectra of these extracts determined in a Beckman DU spectrophotometer. Under these conditions, amphotericin B has a characteristic absorption spectrum with peaks at 363, 382 and 405 μ .¹⁷ Methanol extracts of kidneys of F.C. had absorption spectra with peaks at 360, 382 and 405 μ . Similar peaks were also observed in dimethylsulfoxide extracts. These peaks were not observed following extraction of control human kidneys obtained at autopsy, nor were they found in extracts of kidneys of S.L. which had been previously fixed in formaldehyde for some weeks prior to lyophilization.

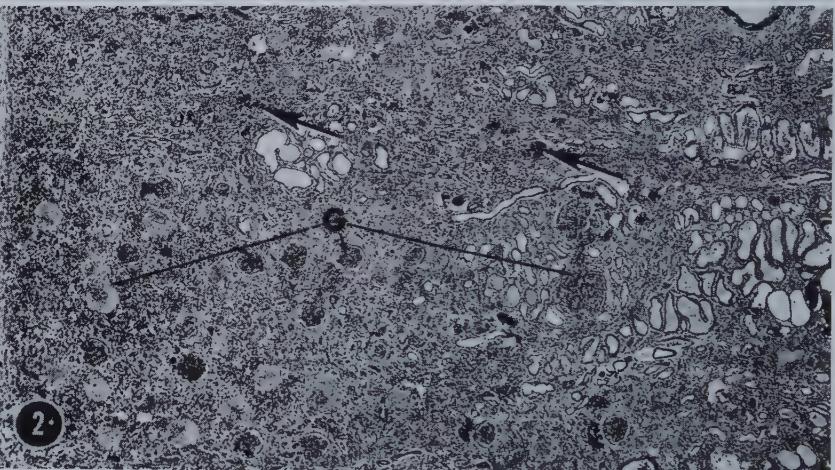
The material presumptively identified as amphotericin B in solvent extracts of kidneys of patient F.C. is present in such minute amounts (less than 0.5 μ g./gm. kidney) that further isolation and identification was not attempted.

DISCUSSION

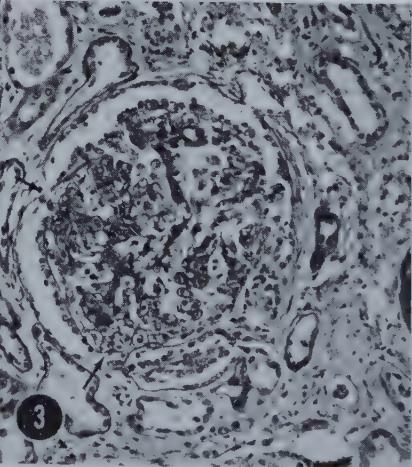
Amphotericin B, a polyene antifungal antibiotic isolated from *Streptomyces* sp., is insoluble in water and most organic solvents.¹⁷ In order for it to be maximally effective for the treatment of systemic mycotic infections, the drug is solubilized by the addition of deoxycholate and administered intravenously.^{6, 18} Blood levels are well maintained following administration by this route, amphotericin B being gradually excreted by the kidney.⁶ Following intravenous administration of large amounts, detectable levels of amphotericin B may remain in body tissues for long periods of time as demonstrated by the presence of minute amounts of spectroscopically demonstrable amphotericin B in the kidneys of F.C. one year after the cessation of treatment. That the drug is stored in body tissues and continues to act on the kidney long after the last dose has been administered where large total doses have been given, is



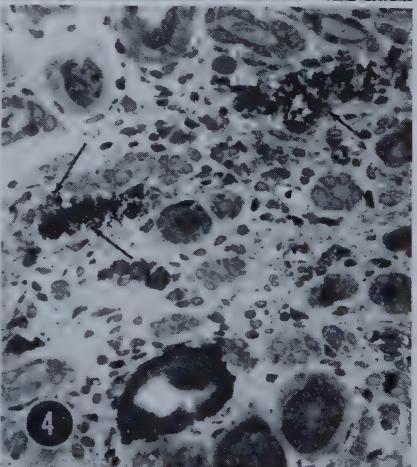
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2



3



4

Fig. 1. 1, Radial section of kidney of patient F.C. Renal capsule is at the left; medulla at right. The large vascular structures in the center are at the corticomedullary junction. Medullary rays (large arrows) are dark due to the presence of calcium deposits within them. Note atrophy in the peripheral cortex and the dilated tubules at the corticomedullary junction and in the medulla. Formol fixation, H & E ($\times 10$).

indicated also by the clinical progression of the renal insufficiency and the active proliferative glomerular lesion and the pattern of tubular calcium deposition observed in the cases described herein. The transiency of renal lesion pursuant to the administration of smaller total amounts of amphotericin B may be dependent upon the ability of the body to rid itself of the drug before kidney function is permanently compromised.

Sensitization to the drug appears to have no role in the pathogenesis of the renal insufficiency resulting from the administration of amphotericin B. No deposits of the patient's globulin were identified in the kidney of patient F.C. using fluorescein labeled anti-human globulin, and there were no demonstrable antinuclear antibodies in the serum of this patient.

The singular involvement of the juxtamedullary glomeruli by hyperplastic and inflammatory changes appears unique when viewed as a result of drug toxicity, particularly since glomeruli located more peripherally in the cortex do not show these changes. On the other hand, glomerulonephritis of man and nephrotoxic nephritis in the experimental animal have been observed to present selective involvement of the juxtamedullary glomeruli.^{3, 11} Calcium deposition in portions of the distal nephron in the cortex adjacent to medullary rays is a second distinctive feature of the renal lesion associated with amphotericin B therapy.^{4, 12} Such a location is similar to that found in experimental animals following the administration of parathormone.¹³

SUMMARY

The renal lesions are described in two patients treated with large total doses of amphotericin B for coccidioidomycosis. The lesions are similar in that: (1) chronic and progressive renal insufficiency has resulted in kidneys which were not significantly reduced in size, (2) there is a slight reduction in cortical width, with an increased prominence of interstitial tissue due to edema and fibrosis, (3) a glomerulonephritis type of pattern involves the juxtamedullary glomeruli, and (4) there are abundant deposits of calcium within tubules of the distal portion of the nephron adjacent to the medullary rays. The chronic or late renal lesion which follows amphotericin B therapy appears to be dose-related, chronic renal insufficiency progressing after cessation of therapy when the antifungal agent is given in large total amounts. In both cases, the lesions appeared

2. Radial section of kidney of patient S. L. Renal capsule at the left; corticomedullary junction at right. Calcium deposits are present in medullary rays (large arrows). Glomeruli (G) vary in size from small fibrotic whorls in the atrophic portion beneath the capsule to hypertrophied tufts and tubular components at the corticomedullary junction. Formal fixation, H & E ($\times 22$).

3. Enlarged glomerulus (600 μ diameter) from kidney of patient S. L. Epithelial cells are prominent. Vascular tuft is enlarged. Adhesions between visceral and parietal layers of Bowman's capsule are indicated by arrows. Increased loose connective tissue surrounds adjacent tubules. Formal fixation, PAS ($\times 80$).

4. A portion of renal corticomedullary ray of patient F. C. Granular calcium deposits in the upper half of the figure occupy tubular lumens. Arrows indicate remnants of epithelium in these tubules. The large oval calcium deposit in the lower half of the figure is not associated with tubular epithelium in the plane of section. Buffered osmium tetroxide fixation, Toluidine Blue O-Alizarin Red S ($\times 300$).

active at the time the kidneys were examined, and in one, traces of amphotericin B were found one year after cessation of treatment.

Acknowledgments

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The Present Status of Respiratory Viruses

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ACUTE respiratory disease continues to be man's most common illness. Although not usually associated with dramatic mortality figures, except during epidemics of influenza, it is an outstanding leader in the various parameters of morbidity. In the United States in a 12 month period ending June, 1959, there were 367.9 million acute conditions involving medical attention or one or more days' restriction of activity. Of these, 215.3 million (58.5 per cent) were due to acute respiratory illnesses, two-thirds of which were diseases of the upper respiratory tract.⁵³ A continuing study of acute conditions reveals the persistence of this relationship, and also shows the well established seasonal relationship of acute respiratory disease with the colder months (Fig. 1).

Acute respiratory disease is the foremost cause of time lost from work, accounting for approximately five and a half days per year per employed person, or about one-third of all time lost.⁵⁵ Likewise, it is the leading cause of school days lost. In a long-term study of patterns of illness among University of Wisconsin students in both clinic and hospital populations, acute infections of the respiratory tract outnumbered all other causes of illness by a substantial margin.¹⁴

Information gathered from sources such as the above does not tell the entire story, however, because it does not include morbidity experienced without time lost or that not requiring medical attention. Since the studies of Dingle et al.,¹³ involving close observation of a study population over a prolonged period of time, the complete picture of acute respiratory illness is becoming apparent. Members of the families observed by these investigators suffered an average of approximately six respiratory illnesses per year, and these accounted for approximately two-thirds of all the illnesses experienced. Their findings have been confirmed by more recent studies in both children and adults. Valadian et al.⁶⁴ followed 134

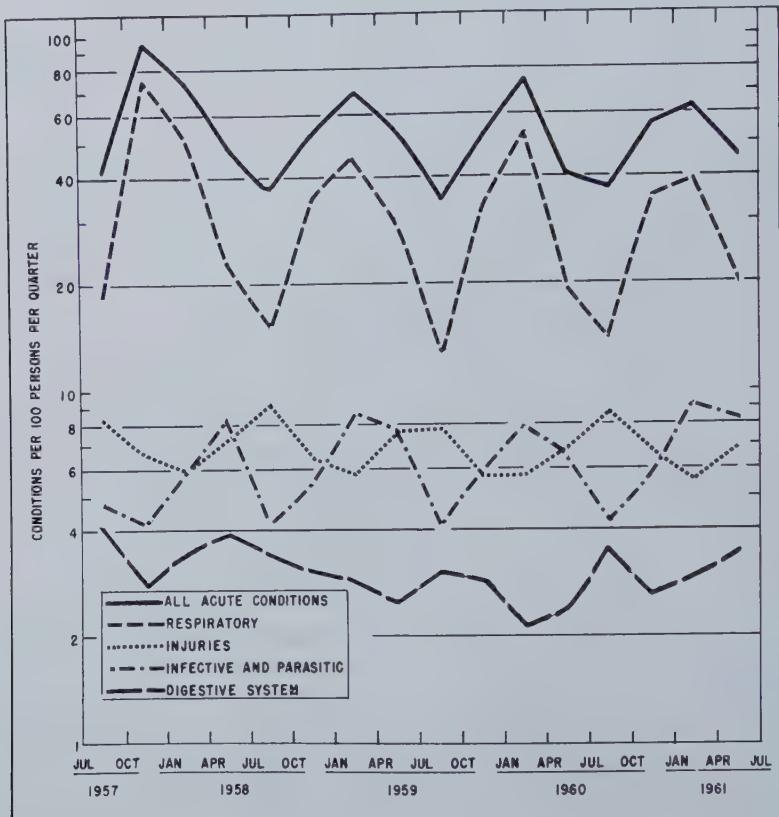


Fig. 1. Incidence of acute conditions per 100 persons per quarter in the United States.
(Reprinted with permission of National Health Survey.⁶²)

"healthy" children from birth to 18 years, and found that acute respiratory illnesses constituted a remarkable 83 per cent of the total illness experienced by the group during this period. At all ages, the percentage of total illness was high, with the pre-school period giving the highest rates and infancy next. There was a higher percentage of severe respiratory infections in the younger ages, from infancy to ten years. This study also showed that, in general, children remained relatively constant in their susceptibility to respiratory infections, some of them being relatively "cold prone."

McNamara et al.³⁹ followed ten "healthy" adults over a nine month period. Acute respiratory symptoms accounted for 47 per cent of all symptoms experienced, and there were 4.5 discrete episodes of acute respiratory disease per person during the nine month period. It was noted that the acute episodes were of a relatively mild, afebrile nature, and that, in the well-motivated group studied, absenteeism was low.

Against this background of plenty, in the form of disease, there has been in the past a scarcity of etiologic agents. Grieble et al.¹⁷ reviewing the subject as recently as 1958, assigned the etiology of acute respiratory disease in adults as follows: 5.7 per cent streptococcal, 13 per cent known

Table 1. Acute Respiratory Disease Viruses

Myxovirus
Influenza: types A, B, C
Parainfluenza: types 1, 2, 3, 4
Adenovirus: types 1-7, 14, 15, 21
Respiratory syncytial virus
Picornavirus
Coxsackie, Group A: types 2, 4, 5, 6, 8, 10, 21 (Coe)
Rhinovirus: types 30 plus
Reovirus: types 1, 2, 3 (? cause of respiratory disease)

viral, and 81.3 per cent unknown viral. In reviewing the progress that has been made in the last few years, it will be seen that the virology of acute respiratory disease is undergoing revolutionary growth. There are now nearly 100 known viruses that have been demonstrated to be capable of producing respiratory symptoms, and approximately 50 different types that now can be considered to be major respiratory viruses.

It has been known for some time that many viruses not considered primarily as respiratory viruses can cause symptoms of acute respiratory disease. A list of these would include varicella, variola, rubella, mumps, polio, coxsackie, ECHO and salivary gland virus. The early, and sometimes only, symptoms of infection with these viruses may be respiratory, and they qualify as respiratory viruses since they usually, or sometimes, are spread by the respiratory route. However, their major manifestations appear elsewhere, and they are not usually thought of as "cold viruses."

The most important human respiratory disease viruses known at present are listed in Table 1. Influenza, the first respiratory disease virus to be isolated and studied, is considered in a separate section of this publication; the others are reviewed briefly in turn.

PARAINFLUENZA VIRUSES

The first virus related to this group was isolated in Japan from a mouse in 1953 and called Sendai agent. In 1955, a parainfluenza virus was first associated with human disease, being isolated from children with croup.⁵ These viruses have the characteristics noted in Table 2. Because of the variability of their cytopathic effect in tissue cultures, work with them has depended on the fact that erythrocytes adsorb to the surface of tissue culture cells infected with these viruses.

Parainfluenza viruses are isolated from the respiratory but not the gastrointestinal tract. Four serotypes are known, although isolations of type 4 have not been frequent. Parainfluenza virus infections are worldwide.^{35, 66} Similar agents also infect various animal species, and a type 3 parainfluenza virus has been shown to produce "shipping fever" in cattle.

The relationship of these viruses to human respiratory disease has been established in both children and adults.^{12, 44} Infections with type 3 are extremely common, and usually occur earlier in life than infections with types 1 or 2. Almost all adults show evidence of having had previous infections with types 1 and 3. Type 1 and 3 infections occur

Table 2. Parainfluenza Viruses

CHARACTERISTICS	CLINICAL SYNDROMES
Size: 90–200 millimicrons in diameter	Types 1 and 3 Children: coryza, pharyngitis, bronchitis, bronchiolitis, bronchopneumonia and croup
Type of nucleic acid: RNA	Adults: coryza
Variable cytopathic effect	Type 2 Children: croup and acute nonspecific febrile illness
Growth in chick embryo	Adults: coryza
Ether sensitive	
Acid labile (pH 3.0)	
Soluble type-specific antigens	
Hemadsorption phenomena	
Agglutination of erythrocytes of certain species (human, guinea pig, chicken)	

throughout the year, while type 2 infections have been more sporadic in occurrence. The incubation period for type 1 infection is five to six days, and for type 3 is two to three days.

In children, these viruses produce a spectrum of clinical illness including rhinitis, pharyngitis, bronchitis, bronchiolitis, bronchopneumonia and croup. There is good evidence that initial infection with these agents leads to more serious lower respiratory tract infection, while reinfection, which occurs both in children and adults, is more apt to cause a coryza-like illness.⁴⁴ Earlier studies had linked type 2 infections in children almost exclusively with croup,³⁴ and although this virus is, undoubtedly, an important cause of croup, recently it has also been shown to produce an acute nonspecific illness in children without predominant respiratory symptoms.³²

In adults, parainfluenza infections have been associated with upper respiratory tract disease of the common cold type.^{12, 41} Inoculation of adult volunteers with type 3 resulted in production of a cold-like illness with mucoserosus nasal discharge, nasal obstruction, sneezing and dry cough.³¹ The volunteers all had pre-existing neutralizing antibodies, indicating that previous experience with this virus leads to a state of partial immunity which prevents severe but not mild acute respiratory illness.

ADENOVIRUSES

Respiratory disease has always been of interest to the military because of its obvious adverse effect on military efficiency, especially recruit training programs. Some of the roots of current progress arise from experiences encountered during World War II. At that time, the Commission on Acute Respiratory Diseases¹¹ described a grippelike syndrome, ARD (acute respiratory disease) which could be distinguished clinically and epidemiologically from the common cold. However, no etiology could be established at that time. In 1953 Rowe et al.⁵¹ isolated the first adenovirus from tissue cultures of human adenoids undergoing spontaneous degeneration, and shortly after this Hilleman and Werner²¹ recovered an adenovirus from military recruits with ARD. With this,

Table 3. Adenoviruses

CHARACTERISTICS	CLINICAL SYNDROMES
Size: 60-80 millimicrons in diameter	Types 1, 2, 5, and 6—Upper and/or ? lower respiratory tract disease, primarily in children and infants
Shape: icosahedron	Types 3, 4, 7, 14 and 21—ARD in military recruits
Type of nucleic acid: DNA	Type 3—Pharyngoconjunctival fever, predominantly in children
Characteristic cytopathic effect	Type 8—Epidemic keratoconjunctivitis
Ether-resistant	Types 3, 6, 7, 10, 15, 16, 17 and possibly others—Acute follicular conjunctivitis
Acid stable (pH 3.0)	Types 1, 2, 3, 5, and 6—? etiologic association with mesenteric adenitis and intussusception in infancy
Soluble group-specific antigen	
Soluble type-specific antigens	
Agglutination of erythrocytes of certain species (rat and/or monkey)	

use of tissue cultures for the study of respiratory viruses had its effective inception.

Adenoviruses have the properties shown in Table 3. Currently there are 28 known human types, and other types have been isolated from several species of animals. On the basis of production of disease, cytopathic effect in cell nuclei, some characteristics of growth, and hemagglutinating ability,* human adenoviruses can be roughly placed into two groups. In the first group are types 1, 2, 5 and 6, which are commonly found latent in adenoids and tonsils, and are common infecting agents in young children. The significance of their overall contribution to acute respiratory disease is probably not great, but in the younger pediatric age group they may be common causes of mild respiratory illness.⁴ Fatal adenovirus infections in infants and young children have been reported,⁹ although widespread confirmation of this is lacking at present.

Recently, evidence has been accumulated to suggest that these agents play an etiologic role in the production of mesenteric adenitis and intussusception in infancy.¹⁶ The common occurrence of infection with these agents without apparent related clinical illness makes such a relationship hard to establish. Evidence for their ubiquity is found in serologic studies of various populations, which show that infections with types 1 and 2 are common in infancy, and progressive in frequency throughout childhood. The same epidemiologic pattern holds true for types 5 and 6, but to a lesser degree.

In the second group, consisting of types 3, 4, 7, 14 and 21, a significant association has been established with acute respiratory disease (ARD) in military recruits in many parts of the world.^{15, 57} Also, type 3 has been associated with outbreaks of pharyngoconjunctival fever which, although similar on clinical grounds, has a slightly different epidemiologic setting, occurring most often in children in summer camps or similar settings.

The clinical picture presented by adenovirus infection in the recruit population, although not subject to differentiation on an individual basis, nevertheless is somewhat distinctive in the full-blown case. The picture is that of incapacitating malaise associated with significant fever,

* Type 4 is an exception in regard to hemagglutination.

pharyngitis and a racking, persistent cough, eventually productive of mucopurulent sputum. Headache, myalgia, rhinitis, conjunctivitis and laryngitis are frequently present but overshadowed by the more distressing symptoms first noted. Because the acute pharyngitis frequently is accompanied by marked erythema of the mucous membranes and the presence of exudate, a throat culture is necessary to exclude beta-hemolytic streptococcal infection. A similar problem in differential diagnosis may occur in civilian populations experiencing an outbreak of pharyngoconjunctival fever. Temperature not infrequently ranges as high as 103° to 104° F. and fever lasts about five days. Rhonchi and coarse rales are common physical findings, and approximately 15 per cent of patients will have radiographic evidence of pneumonia. However, this percentage is open to some question at present, and should be clarified by further studies with Eaton PPLO. Incidence of significant illness in recruit populations due to adenovirus has been reported from 38 to 74 per cent, and it is undoubtedly an important agent in this setting. Milder and subclinical adenovirus infections also occur in a large percentage of recruit populations not seeking medical attention. Unlike the first group, the second group of adenoviruses (types 3, 4, 7, 14 and 21) is an insignificant cause of illness in civilians, except as noted in schools and summer camps. Multiple surveys have placed the incidence of adenovirus-caused respiratory illness in older children and young adult civilians at around 3 to 5 per cent per year.

Studies of ARD and pharyngoconjunctival fever have revealed that certain findings may occur as isolated clinical manifestations of infection. One of these, acute follicular conjunctivitis, has been associated with types 3, 6, 7, 10, 15, 16, 17, and possibly others.

An off-shoot of adenovirus investigations has been to establish an etiologic role for type 8 in epidemic keratoconjunctivitis. This is an acute follicular conjunctivitis with accompanying subepithelial corneal opacities which sometimes leads to persistent visual impairment.²⁰

Another recent finding has been that types 12 and 18 will produce malignant tumors in newborn hamsters.⁶⁰ There is no evidence at present that adenoviruses are oncogenic in man, but this will be a difficult fact to confirm or deny.

Most of the higher numbered types of adenoviruses have been isolated from the gastrointestinal tract as opposed to those types mentioned above which are predominantly of respiratory origin. What relationship these more recently discovered adenoviruses may have to human disease remains uncertain at present.

RESPIRATORY SYNCYTIAL VIRUS

This virus was first isolated from a chimpanzee with coryza in 1956.⁴³ In the following year it was isolated from infants with acute respiratory illness.⁶ It has the characteristics noted in Table 4. Respiratory syncytial (RS) virus has appeared to be a single species, although recent evidence has indicated that there may be antigenic differences among various strains.¹⁰ It is difficult to work with this organism because of its poor survival with freezing and its fastidious

Table 4. Respiratory Syncytial Virus

CHARACTERISTICS	CLINICAL SYNDROMES
Size: 90-140 millimicrons in diameter	Children: bronchiolitis, bronchopneumonia, coryza
Synecytial or pseudo-giant cell formation	Adults: coryza
Ether-sensitive	
Acid-labile	
Easily inactivated by freezing	
Soluble complement-fixing antigen	
No hemagglutination demonstrated	

growth requirements. Although syncytial changes in tissue culture are characteristic of this virus, these changes occur only under certain conditions of growth, and other viruses, notably parainfluenza types 2 and 3, may also produce syncytial changes in tissue culture. It has been isolated solely from the respiratory tract.

RS virus infections tend to recur in epidemic form, but occasional sporadic cases are noted. Infection with this virus has been described in many parts of the U.S. and abroad.^{1, 30, 53} Over half of children by age four have evidence of previous infection with RS virus, as do approximately 70 per cent of older children and 100 per cent of adults.³⁷

RS virus has been etiologically linked with acute respiratory disease in both children and adults.^{3, 7, 19, 28} It appears to be the single most important cause of serious lower respiratory tract infections in infants and young children, occasionally producing fatalities.¹ The clinical picture presented in hospitalized infants and young children is that of bronchiolitis and bronchopneumonia. Fever, average maximum rectal temperature 103° F., coryza and cough are common. Pulmonary findings consist of unilateral or bilateral moist crepitant inspiratory rales and decreased breath sounds.³⁰ Distinguishing clinical characteristics, however, are not present. Adams² has noted the possible relationship of RS virus infection and inclusion body, giant cell pneumonia in infants. Milder forms of RS virus infection also occur in children, presenting as acute febrile upper and/or lower respiratory disease.

In adults, natural infection represents a re-exposure to this virus and presents as an acute nonspecific respiratory illness. Inoculation of adult volunteers has produced an afebrile coryzal illness lasting four to seven days which is indistinguishable from the common cold.

COXSACKIE A-21 (COE VIRUS)

In 1958 Lennette et al.³⁶ isolated a virus from patients with colds or pharyngitis which they named Coe virus. Later this agent was found to be antigenically the same as Coxsackie A-21 virus, a member of the enterovirus group. However, Coe virus is an "enterovirus" that in reality has characteristics of a respiratory virus and that can be thought of as a bridge between these two groups. It has the characteristics shown in Table 5. It has been found in various areas of the

Table 5. Coxsackie A Viruses

CHARACTERISTICS	CLINICAL SYNDROMES
Size: 28 millimicrons in diameter	Types 2, 4, 5, 6, 8, 10—Herpangina in children
Shape: dodecahedron	Type 21 (Coe)—ARD in military recruits and similar illness in civilian adults.
Type of nucleic acid: RNA	
Ether-resistant	Coryza
Acid-stable (pH 3.0)	
Cytopathic effect not characteristic	
Type-specific antigens	
Agglutination of human erythrocytes (Coe)	

world.^{38, 46, 65} Isolation is achieved from both rectal and pharyngeal swabs, although the latter yields a much higher percentage of recovery.²⁷ Enteric capsules containing Coe virus have failed to cause infection when given to adult volunteers.⁵⁶

The epidemiology of Coe virus infection appears to be similar in some ways to the group of adenoviruses containing types 3, 4, 7, 14 and 21. Incidence of infection and illness due to this agent appears to be small in children.⁴⁶ In civilians Coe virus is associated with a low serologic conversion rate at any age,⁶⁷ with the highest incidence in young adult males.⁴⁶ This may reflect the fact that Coe virus infection seems to be primarily a disease of military recruits. That it is related to acute respiratory illnesses in these populations is definitely established,²⁷ with evidence that it is responsible for approximately 10 per cent of hospital admissions in some instances.³⁸ However, the occurrence of Coe virus infections appears to be more sporadic than adenovirus infections. The resulting illness reflects a syndrome of acute febrile or nonfebrile respiratory disease in the adult. Hoarseness, headache, and chills have been more prominent in virus positive individuals and cough less prominent, but a differential diagnosis in an individual patient cannot be established. Gastrointestinal symptoms have been noted infrequently. The duration of illness has been five to 12 days. For each reported virus positive illness, there are approximately eight other infections in the group at risk.²⁷ Evidence to date reveals that the presence of neutralizing antibody against Coe virus may lower the probability of illness but does not necessarily protect completely.³⁸

Several other types of group A Coxsackie viruses produce the upper respiratory illness, herpangina, which occurs in epidemics during the summer months primarily in children. This entity is unique among acute respiratory illnesses in having the characteristic physical finding of small (1 to 2 mm.) vesicles on the anterior pillars of the fauces, soft palate and uvula. These progress to ulceration. Such lesions, however, may not be present in all cases. Other features of this illness are dysphagia, fever (range 101° to 105° F.), anorexia, fatigue, abdominal pain and headache. Recovery occurs usually in two to six days.

RHINOVIRUSES

The first virus in this group was isolated in the U.S. in 1956,^{45, 47} and although currently classified as ECHO-28 in the enterovirus group, it has the characteristics of a rhinovirus. Similar viruses were also isolated by Tyrrell et al.⁶¹ in England, and Hamparian et al.,¹⁸ Hamre and Procknow¹⁹ and Johnson and Rosen²⁹ in the United States. These agents were given a confusing number of names including muriviruses, Salisbury viruses, coryzaviruses, and unclassified respiratory viruses. Recently, the International Committee on Virus Nomenclature has proposed that all viruses of this similar small size (Pico) and ribose nucleic acid (RNA) composition be designated as Picornaviruses. This group, therefore, includes Coxsackie viruses, ECHO viruses, and these newly isolated agents that have been given the proposed name of rhinoviruses.

The characteristics of rhinoviruses are shown in Table 6. Work with these viruses has been made possible through a number of modifications of tissue culture techniques including control of pH (7.3 to 7.0), reduced temperature (33° C.), and continuous motion in roller drums. Initial isolation has been greatly facilitated by the introduction of tissue cultures of human embryonic lung fibroblasts which have a diploid karyotype. These possess the characteristics of normal, nonmalignant cells, and have a limited growth potential. Following isolation, the viruses may then be passed to cell lines which have the characteristics of malignant growth and are of a continuous nature. Rhinoviruses may be divided into two groups: H strains which grow only in human cell lines, and M strains which grow in both human and monkey cell lines.³³ These viruses have been isolated from the respiratory tract but attempts at isolation from stool specimens have been unsuccessful.

At present, there are over 30 distinct serotypes, and most certainly others will be discovered in the future. Although antigenic similarity between some serotypes has been reported,⁴² most investigators have found them to have no immunologic relationship.^{33, 58} Evidence to date with some serotypes of rhinovirus suggest that they possess antigenic stability from year to year. The incidence of infection with a particular serotype appears to be infrequent but progressive during childhood, and common by adulthood.⁵⁴

Rhinoviruses have been established as a cause of acute respiratory illness in both adults and children.²³ The clinical picture in children has varied from the common cold to croup, bronchitis and bronchopneu-

Table 6. Rhinoviruses

CHARACTERISTICS	CLINICAL SYNDROMES
Size: 18-28 millimicrons in diameter	Types—30 plus
Type of nucleic acid: RNA	Children: coryza, croup,
Ether-resistant	bronchitis, and bronchopneumonia
Acid-labile (pH 3.0)	Adults: coryza
Cytopathic effect not characteristic but enhanced by growth in roller drum	
Some strains require decreased temperature (33° C.) for initial growth	
Type-specific antigen	
No hemagglutination demonstrated	

monia. However, at present, they do not appear to be a frequent cause of serious respiratory illness in infants and children. Further investigation is needed to establish their true significance.

They have been shown to be a frequent cause of the common cold syndrome in civilian adults, and in military populations, and it is in this context that they appear to be most important. In adults they have been associated only with upper respiratory infections, and there have been no characteristic clinical features of the illnesses produced. In general, specimens of blood taken in the acute phase of illness have shown low or negligible neutralizing antibodies to the infecting virus. Convalescent specimens have usually shown a rise of neutralizing antibodies which is relatively low, but may be high. The frequency of reinfection with a given type has not been determined, although studies using infectious nasal secretions in volunteers would suggest that immunity does not last over one to two years.²⁵ On this basis the possibility of frequent occurrence of reinfection would appear good.

REOVIRUSES

The reoviruses have not been definitely established as a cause of acute respiratory illness in humans. However, there has been enough suggestive evidence, so that they cannot be excluded at the present time. The first virus of this group was isolated from the stools of healthy children in 1954. Since then, isolation has been achieved from both healthy and ill humans as well as various animal species.

These viruses were originally considered to be enteroviruses and the first prototype was given the designation of ECHO type 10. However, because of differences in size and other characteristics, Sabin⁵² proposed that they be removed from the enterovirus group and placed in a new group termed reovirus (respiratory orphan virus) to stress their association with both the respiratory and enteric tracts. There are three serotypes. They have the characteristics shown in Table 7. Virus isolation has been achieved from both rectal and pharyngeal swabs, but more readily from the former. Evidence of world wide prevalence to type 3 has been shown,⁴⁸ and most adults have neutralizing antibodies.

The illnesses that have been most frequently associated with recovery of reoviruses in the United States have been of a mild febrile nature with

Table 7. Reoviruses

CHARACTERISTICS	CLINICAL SYNDROMES
Size: 75 millimicrons in diameter	Types 1, 2, 3—Questionable association with acute respiratory, gastrointestinal and nonspecific illness in children and adults
Shape: icosahedron	
Type of nucleic acid: RNA	
Ether-resistant	
Acid-stable (pH 3.0)	
Cytopathic effect characteristic	
Group-specific antigen	
Type-specific antigens	
Agglutination of human erythrocytes	

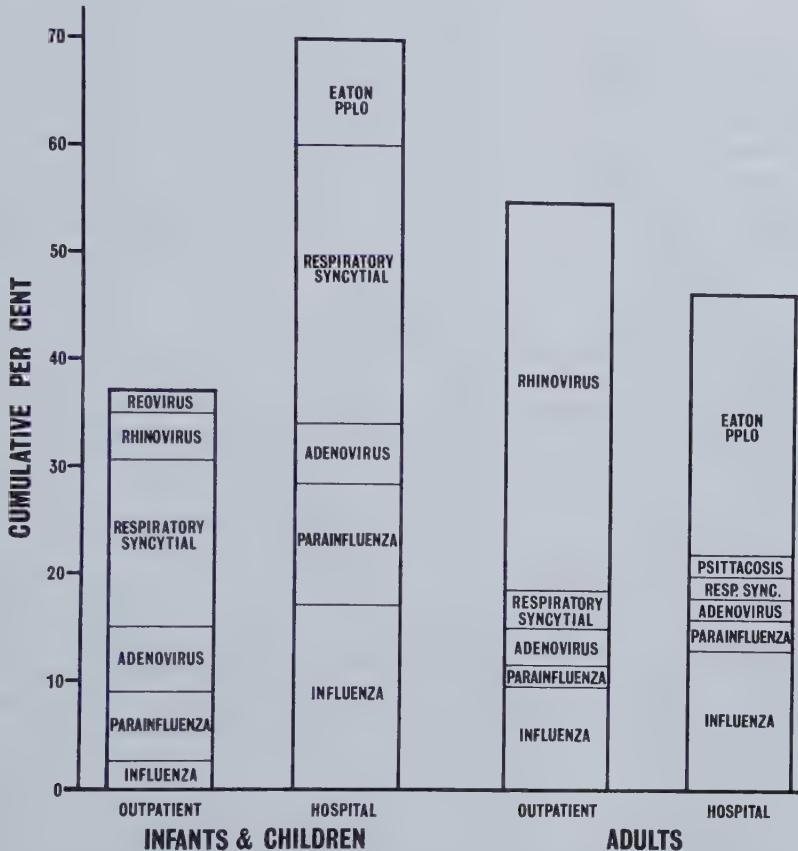


Fig. 2. Overall estimate of relative importance of acute nonbacterial respiratory disease agents according to age and to case selection. (Adapted from Hilleman et al.²³)

coryza and diarrhea.⁴⁹ However, statistical analysis has yet to establish an etiologic association between reovirus infection and naturally occurring illness in humans. Volunteer experiments in adults with all three serotypes have failed to produce illness which could be definitely attributed to the viruses inoculated.⁵⁰ Knowledge of the true significance of reoviruses in acute respiratory disease must await further investigation.

DISCUSSION

Recent progress in determining the etiology of acute viral respiratory disease has been spectacular. We may now reasonably ascribe a combined etiology to approximately 50 per cent of illnesses at all ages, with higher percentages for selected populations (Fig. 2). It has become increasingly evident that virus, host and environmental factors produce different etiologic patterns for different population groups. Influenza is somewhat of an exception in that it attacks all populations with frequency although

highest attack rates occur in school children. The young adult in a military population is particularly susceptible to adenovirus and Cox-sackie A-21 infections. A major part of acute respiratory illness in infants and young children is caused by respiratory syncytial virus and parainfluenza viruses. The adult civilian appears to be the primary target for rhinoviruses, although further study may show these agents to play a bigger role in other populations. Environmental factors have been studied intensively but, at the present time, our only certain knowledge is that winter months are associated with more acute respiratory disease than summer months.

It is also becoming increasingly apparent that a particular virus may cause a wide range of clinical syndromes, and conversely a particular clinical syndrome may be caused by a number of viruses. Simultaneous infection by more than one virus can occur.³⁸ At present, a differential diagnosis is usually impossible on clinical grounds, although an educated guess based on statistical probabilities in a selected population may have value. There is good evidence that initial infection with a particular virus will usually lead to more serious illness than reinfection with the same agent. This seems to be a common event with many respiratory viruses. This agrees with the clinical observations of more severe lower tract infections in infants and young children and of milder upper respiratory infections in older age groups. In view of the known occurrence of reinfection, protection afforded by infection with these agents would seem to be incomplete and not long lasting. Thus far, the more recently discovered respiratory viruses have been antigenically stable. Recurrent changes, as occur with the influenza virus, have not been observed, although only observation over a longer period of time will reveal the true degree of antigenic stability.

Treatment

Treatment of acute viral respiratory disease remains symptomatic. Primary atypical pneumonia caused by Eaton agent, a pleuropneumonia-like organism, responds to certain antibiotics; this disease is considered in another section of this issue. Work on antiviral drugs has made some progress but, as yet, there is no indication that any effective therapeutic agent is in sight. Continued evaluation of antibiotic therapy in regard to virus-caused respiratory disease⁵⁹ fails to show any beneficial effect on the initial illness or the prevention of complications. The indication for antibiotic therapy remains the demonstration of an antibiotic-sensitive bacterial infection complicating the original condition. Antihistamine compounds continue to enjoy widespread use, although their value in preventing or aborting acute respiratory infections has never been established.

VACCINES. At the present time, the major hope for controlling acute respiratory disease lies in the development of effective vaccines. Because of the multiplicity of respiratory viruses and the relatively poor antigenicity of some, this presents many problems. Effective vaccines against respiratory viruses have been produced as in the case of influenza vaccine, now an established tool of medicine. There has also been consider-

able work on the development of adenovirus vaccines. These have been either bivalent, containing types 4 and 7, or trivalent, containing types 3, 4 and 7. Field trials in military populations employing these vaccines have resulted in a reduction in febrile respiratory illness, from all causes, of 55 per cent to 81 per cent. When refined rates for illness caused by adenovirus alone were calculated, reduction by 90 to 98 per cent by the bivalent and 83 per cent by the trivalent vaccines was achieved.²² Recently, these vaccines have not been available because of the discovery of endogenous wild viruses in the tissue culture material used for vaccine production. However, this is a technical problem which should not prevent their use in the future. An effective vaccine has been produced combining both influenza viruses and adenoviruses.⁴⁰ Adjuvant was included in the composition of this vaccine to induce greater rises in antibody titers, and appears to be effective and safe in humans. Other workers have shown that it is feasible to produce a vaccine from formalin-treated parainfluenza viruses which is potent and safe in adults, children and infants.²⁶

It has been suggested, because of the large number of etiologic agents responsible for acute respiratory disease, that vaccines be tailored to suit various populations.²⁴ Thus, when evidence has been obtained that certain populations are deficient in antibodies to viruses which are common pathogens for such a population, they would be given a vaccine which would fill their "immunologic gaps." The use of adjuvant would also appear to be helpful in the development of vaccines since it enhances potency while reducing inoculum volume, a definite consideration in view of the multiplicity of respiratory viruses. Currently, there is interest in the development of a vaccine for the viruses which cause serious lower respiratory tract illnesses in infants and young children, parainfluenza and respiratory syncytial. Production of such a vaccine will probably lead to the first widespread effort to control some of the newly discovered respiratory viruses. The next, and undoubtedly more difficult step, will be the development of a rhinovirus vaccine to control common colds in adults.

SUMMARY

Acute respiratory disease is the greatest cause of morbidity in man. Recent years have seen the discovery of a number of viruses which cause acute respiratory illness in man and also in animals. These agents have been primarily identified by the effect they produce in tissue culture cells.

The frequency of acute respiratory disease appears to be due to at least two factors. First, there are a large number of etiologic agents, and second, they have a poor ability to evoke long-lasting complete immunity following infection. This appears to be due to the demonstrated low level of initial antibody response, and the relatively short duration of effective antibody levels. The latter is somewhat speculative at present. Natural reinfection with these agents does occur, however, and there is no reason to believe that it is uncommon. Periodic changes of the antigenic com-

position of these more recently discovered viruses has not been noted as yet, and does not appear to be a factor in the frequency of occurrence of acute respiratory disease.

Different population groups tend to be attacked by different respiratory viruses. Infants and young children have more frequent and more severe lower respiratory tract illnesses. This is in part due to the fact that initial infection with a respiratory virus tends to cause more severe illness than does reinfection. A particular respiratory virus can cause a variety of clinical syndromes varying from mild to severe illness. A particular respiratory syndrome can be caused by a number of different viruses.

Excepting Eaton PPLO pneumonia and diseases of bacterial etiology, the treatment of acute respiratory disease remains symptomatic. Although the large number of viruses and their relatively poor antigenicity present difficult problems, there is reasonable hope that the future will see the gradual development of effective vaccines to control acute respiratory illness.

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The Role of Immunity in the Common Cold and Related Viral Respiratory Infections

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THE SYNDROME of the common cold is the most frequent and recurrent of man's ills, and for many years it was believed that immunity to the disease did not result from infection. There was good reason for the belief from epidemiologic data which showed that colds seemed to follow one another relentlessly. One set of observations in this regard is shown in Figure 1 which illustrates the absence of any discernible period of protection from natural colds following an experimentally induced common cold. The average time elapsed before a second cold occurred in 50 per cent of the group was 6.3 weeks and none of the subjects remained free from a second common cold beyond 22 weeks. The earliest volunteer studies with nasal secretions bore out this same impression.⁸

On the other hand, the point of view that immune mechanisms are important in one's susceptibility to common colds, but that multiple etiologic agents are at fault is suggested by other epidemiologic observations. Among such isolated groups as on Spitzbergen in the Arctic ocean,³⁷ common respiratory diseases have been observed to decrease markedly during the period of isolation, then occur in epidemic waves following

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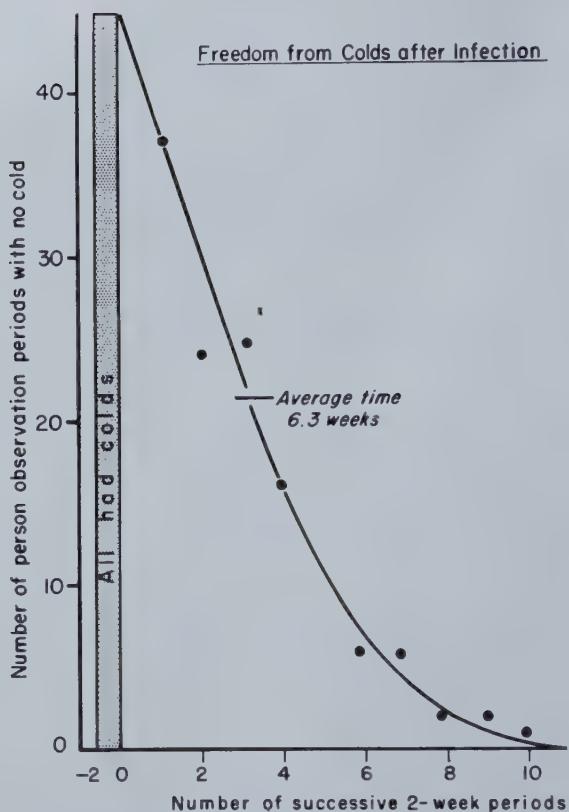


Fig. 1

contact with newcomers. Also, the frequency and severity of colds tend to diminish with age.

It was generally assumed until recently that the common cold was caused by a single virus. Under such an assumption infections appeared to be incapable of activating the protective mechanisms of the host, even for a few weeks. In the past few years, however, a large number of viruses have been recovered from persons with the common cold syndrome. Many of the viruses have been isolated in tissue culture or laboratory animals and studied carefully and extensively. Others have been demonstrated only by the production of colds in volunteers with bacteria-free filtrates of nasal secretions. It is thought that most or all of these viruses are the etiologic agents of the colds that annually affect a large proportion of our population. Thus, no single agent is exclusively responsible for the common cold although some of these viruses can cause other respiratory syndromes as well as the common cold.¹¹ Upon this basis, immunity to the common cold and other viral respiratory infections would be specific for each virus and in some cases for each strain of virus. Even considering the large number of agents known to cause colds and the unknown agents yet to be identified, the frequency of the syndrome must still be accounted for in any concept of protective immunity to cold viruses. It must be

determined whether the protection conferred by infections with these agents is transient or incomplete or both.

KNOWN ETIOLOGIC AGENTS

Among the known viruses, those most likely to cause the common cold syndrome as the primary manifestation of infection are some small viruses that have been reported as rhinoviruses, coryzaviruses, muriviruses or unclassified common cold viruses. Included among them, one of the first to be identified was strain 2060-JH (ECHO 28). The common cold syndrome in man also is known to be caused by Coxsackie virus type A-21 which was originally called Coe virus, the respiratory syncytial virus and the parainfluenza viruses. Type 1 reovirus has been recovered in nasal secretions but its etiologic relation to the common cold is not established. Colds have also been associated with some types of adenoviruses which usually cause pharyngitis, the influenza viruses and some true enteroviruses including several ECHO strains. How many more agents that might be responsible for the complex illness we term the common cold and remain to be found and characterized is not known.

SERUM ANTIBODY FROM NATURALLY ACQUIRED INFECTION

Rising serum antibody titer is an accepted index of a virus infection. It is thought to be a protective reaction on the part of the host. Owing to the impression that prevailed until recently that protection against colds seemed to be deficient, a review of serum antibody levels against some respiratory viruses is of interest. Table 1 summarizes serologic data from clinical illnesses in which the indicated viruses were recovered. The number of fourfold or greater rises in antibody is compared with the total number of cases in which virus was isolated. In most studies, a number of significant antibody responses also occurred in persons from whom virus was not recovered but, to avoid uncertainty, these cases have been omitted from the tabulation.

Table 1. Rising Titers of Specific Antibody After Natural Infections in which the Virus was Recovered

VIRUS	NUMBER OF SUBJECTS	PER CENT WITH FOURFOLD INCREASES IN ANTIBODY TITER	REFERENCES
Respiratory syncytial...	31	90	6, 29
Parainfluenza 1.....	80	81	7, 9, 32, 36, 54
Parainfluenza 2.....	36	72	10, 28, 35, 36, 54
Parainfluenza 3.....	91	77	7, 9, 32, 36, 54
Coxsackie A-21.....	106	60	3, 26
Rhinovirus group.....	20	70	15, 39, 50
Adenovirus group.....	37	95	14, 25, 47, 52, 53
ECHO 11.....	3	100	43
Reovirus 1.....	5	20	43

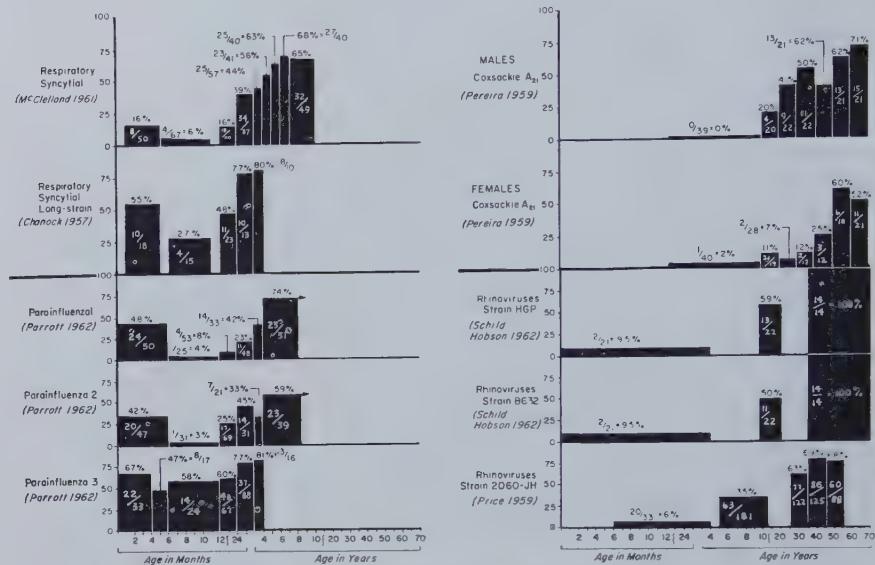


Fig. 2. Prevalence of identifiable serum antibodies in a selected population (see text).

The table shows that recovery of an adenovirus from subjects was attended by significant antibody rises in 95 per cent of the cases tabulated. The parainfluenza and respiratory syncytial viruses are also seen to produce significant rises in the specific antibody titer. Coxsackie A-21 and the rhinovirus family seem to be less frequently associated with serologic response. The data on ECHO 11 and reovirus are insufficient for evaluation.

In Figure 2 the prevalence of identifiable serum antibody in a selected population is indicated by a bar delineating the age limits for the group reported. The height of the bar corresponds to the prevalence of antibody. The most striking feature of the figure is the presence of antibody in so many people, often developing very early in life. It is an accepted assumption that all these people had infection with each of the viruses or infection with an antigenically closely related virus. The patterns suggest that there is some permanence to the antibody, as the prevalence rises steadily with age except in the first six months of life when maternal antibody is disappearing. Reinfection and possibly recurrent illness rather than permanent immunity, however, could be the mechanisms for the persistence of antibody. The differing rates of antibody acquisition to different viruses suggest a difference in the transmissibility of the viruses. This may either result from the properties of the virus or be related to the environmental differences and the social traits of the host.

THE PROTECTION AGAINST NATURALLY ACQUIRED INFECTION AFFORDED BY SERUM ANTIBODY

In view of the observations that in many instances serum antibody rises in response to an infection, the question is whether the height of the titer of antibody can be correlated with protection of the host against

Table 2. Relation of Preinfection Serum Antibody in Persons who Developed Natural Infection

VIRUS	NUMBER OF SUBJECTS FROM WHOM VIRUS WAS RECOVERED	PER CENT WITH PRE-EXISTING SERUM ANTIBODY*	REFERENCES
Respiratory syncytial.	64	30	6, 16, 29
Parainfluenza 1.....	45	2	7, 9, 12, 32, 54
Parainfluenza 2.....	17	0	7, 28, 54
Parainfluenza 3.....	39	18	7, 9, 12, 32, 54
Coxsackie A-21.....	33	3	3
Rhinovirus group.....	149	12	15, 34, 39, 50
Adenoviruses.....	43	7	14, 25, 45, 47, 52, 53

* The criterion for significant levels of pre-existing antibody is that set by the authors' reference.

another infection with the same virus. The efficacy of antibody can be evaluated by the prevention or modification of illness, or by the prevention of infection altogether as observed by the inability to recover virus after exposure of the host to it. Clinically, the former is of paramount importance, yet the latter may be a better guide to the role of antibody in immunity and the mechanism of antibody persistence.

In Table 2 an attempt is made to learn the degree of protection conferred by antibody as observed in retrospective studies of illness caused by each of several viruses. The cases selected were those in which a virus was recovered.

The values reported in the table are expressed as the number of persons having antibody titers above a level selected by each of the authors compared with the total number of ill persons studied from whom a virus was recovered. Only 2 of 62 cases of infection with parainfluenza viruses types 1 and 2 occurred in persons with an antibody titer equal to or greater than 1:8. Similarly, 97 per cent of the observed natural infections with Coxsackie A-21 virus occurred in people without specific antibody, 93 per cent of adenovirus infection and 88 per cent of infections with the rhinoviruses. Serum antibody against parainfluenza type 3 virus and respiratory syncytial virus appeared less protective in that 24 and 28 per cent of cases respectively occurred in persons with serum antibody. These data include both complement fixing and neutralizing antibody but the former are often not correlated with protection. In the sample available, however, the inclusion of complement fixing antibody did not appear to be the basis for the poor protection observed against the infections. The small number of cases available for this type of analysis makes a final judgment of significance difficult.

A prospective study by Chanock et al.,⁴ as summarized below, is very helpful in evaluating the effect of pre-existing antibody against a natural rechallenge with parainfluenza 3 virus.

In three successive outbreaks of parainfluenza 3 infection at Junior Village, a welfare nursery home in Washington, D.C., a number of children were present

during more than one round of infection. These outbreaks occurred in the following time sequence during 1958-1959: December 27 to February 4, March 27 to April 17, and May 20 to August 15. During the first outbreak the virus was recovered from 49 of 85 children in the home, or 58 per cent. Of those who were infected, 36 were present during the second outbreak, among whom 7 (19 per cent) became reinfected. During the third outbreak, 25 were still present of whom 4 or 16 per cent became reinfected. No triple infections were observed. The reinfection rate, therefore, appeared to be one-third the initial infection rate. During the second and third outbreaks respectively, 19 of 71 children had infection and among them 2, or 10 per cent, became reinfected compared with 42 among 140 or 30 per cent of all of the children present. Thus the data from the last 2 outbreaks corroborate the two-thirds reduction in the infection rate following prior infection as noted among the children present from the start.

Febrile illness occurred in 9 of 16 on the first infection. All 9 had neutralizing antibody titers of 1:16 or less before the infection. Upon reinfection, the period during which the virus was shed was generally shorter; febrile illnesses occurred in only 2 instances, and in both cases fever lasted only 1 day. The second infection produced a fourfold antibody titer rise in 10 of the 15 children, suggesting that a new infection had been present rather than a virus carrier state.

The effect of antibody on illness was apparent when data from all the outbreaks were combined. Infection developed in 54 children with a neutralizing antibody titer of 1:8 or less. Of these, 78 per cent were febrile and one-third had lower respiratory tract symptoms and signs. Among 18 children who became infected although the antibody titer was between 8 and 32, only 33 per cent had febrile illness. Of 43 virus recoveries from children in whom the antibody titer was 64, only 19 per cent were associated with fever. Symptoms of lower respiratory tract infection occurred in only 4 of 61 infections (7 per cent) in children with titers higher than 1:8 as compared to the 33 per cent occurring when the antibody titer was lower.

These findings illustrate that, although serum antibody is not completely protective, it does appear to be related to immunity. The pattern of immunity observed conforms to the hypothesis that prior infection with a respiratory virus elicits an antibody response and reinfection, if it occurs, tends to produce successively milder illnesses.

VOLUNTEER STUDIES WITH NASAL SECRETIONS

Studies in volunteers using nasal secretions from common cold donors as the infectious challenge also showed that colds resulted from infection with a number of different etiologic agents.²¹ These differences were evident in the variation in the incubation periods of the colds and to some extent in the clinical syndromes, but the principal and most significant evidence of difference was in the high level of specific immunity acquired against rechallenge with the same virus.¹⁸ In Figure 3 the results of the first and second challenges with each of four nasal secretions are shown. In each case there is a highly significant reduction in the number of colds after the second challenge with the same secretion as compared with the first. That the results were not caused by some nonspecific factor or a decrease in the infectivity of the challenge inoculum was shown by adequate controls. For instance, some volunteers received a different secretion for rechallenge than for the original challenge and other volunteers were challenged for the first time simultaneously with the same

SPECIFIC IMMUNITY UPON RECHALLENGE WITH EACH OF FOUR NASAL SECRETIONS

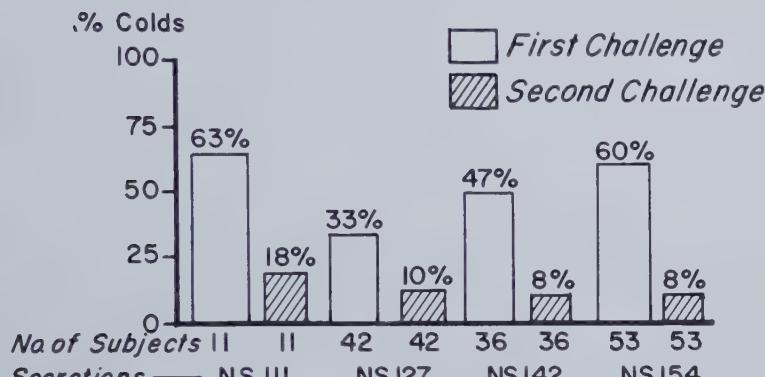


Fig. 3

RECHALLENGES WITH INFECTIOUS NASAL SECRETIONS IN VOLUNTEERS

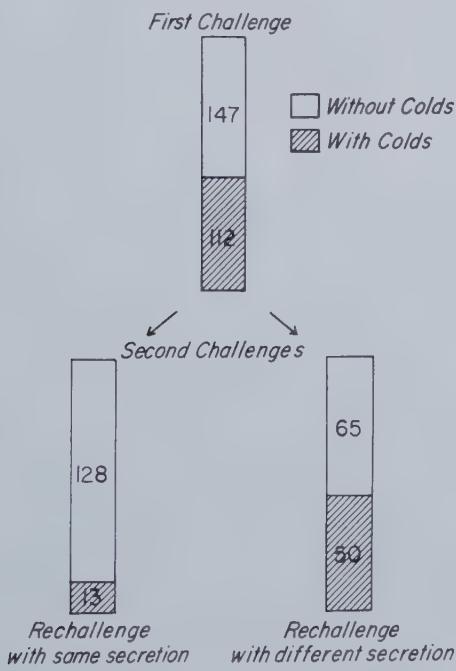


Fig. 4

inoculum used in the rechallenge. The results of rechallenge in the same individuals are shown in Figure 4. The direct evidence obtained by successive challenges of subjects with a measured dose of infectious material under controlled circumstances established beyond any reason-

able doubt the development of immunity by prior infection with a common cold virus and emphasized the specific nature of the immunity.

That the basis for the immunity might be circulating antibody elicited by specific antigenic components of the virus was also suggested by the observation that preincubation of the virus with pooled human gamma globulin neutralized its infectivity for volunteers.²⁰ A decrease from 52 to 10 per cent in the proportion of volunteers developing colds was demonstrated. The use of serum albumin rather than gamma globulin had no effect, and boiling the gamma globulin destroyed its effect.

Demonstration that the gamma globulin in the circulating plasma was transferred to the locus of infection in the surface membrane of the nose also was obtained.² The mechanism is probably one of hyperemia and exudation but virus infection was observed to initiate the process before the onset of clinical symptoms from infection. Gamma globulin, which is not normally present in nasal secretions, appeared and asymptomatic infections were observed. Such observations make a logical basis for the impression that recurrent infections of the respiratory membrane can occur with mild illness or none at all; such infections may serve as a periodic booster stimulus to specific antibody.

The duration of the immunity after infection was observed by rechallenge for as long as 44 weeks, which was the longest period tested. Further information was obtained by testing the neutralization of infectious secretions for volunteers by serum taken at intervals from two subjects at different periods of time after an experimentally initiated infection with the secretions to be tested.¹⁹ Serum taken one month after infection reduced the incidence of colds in new volunteers only from 35 per cent to 30 per cent, but serum taken six and 12 months after infection reduced the incidence of colds to 9 or 10 per cent. By 18 months after infection the neutralizing capacity of the serum was still demonstrable but weaker, and after 24 months the serum had lost most of its ability to alter the infectivity of the secretion. From these observations, it would appear that the duration of immunity after a common cold may be on the order of two years, without the stimulus of reinfection. As the level of protection falls, reinfection is likely, and the severity of the illness may be related to the time since the previous infection.

In order to observe whether a correlation existed between the observed effect of time on the neutralizing capacity of serum after infection and the susceptibility of volunteers upon rechallenge, studies were done on volunteers at three to four weeks after the initial challenge and after three to four months.¹⁹ The incidence of colds was reduced from 31 per cent in the first challenge to 17 per cent following rechallenge at three to four weeks. When the second challenge was postponed until three to four months after the initial infection, the incidence of colds was reduced to 4 per cent.

Although these results apply only to the particular virus tested, they form an integral pattern that may be quite general for the common cold viruses. The essentials of the pattern are that immunity can be demonstrated either by direct rechallenge or the development of neutralizing

capacity in the gamma globulin fraction of the serum. The development of solid immunity from a common cold is not as prompt as from systemic infections or following intramuscular injection of antigens, but the strength of the immunity increases over a period of a few months and then wanes. Reinfection with most of the respiratory viruses is probably frequent but modification or prevention of illness by the exudation of specific antibody into the nasal secretion is likely. In the absence of reinfection the duration of immunity appears to be about two years.

VOLUNTEER STUDIES WITH KNOWN AGENTS

Studies in volunteers have now been carried out with several known viruses. Such studies have utilized tissue culture harvests of virus, which may differ in their infectivity and capacity for antigenic stimulation compared with naturally-occurring strains of virus. Infectivity and illness observed in these studies are related to the dose and attenuation of the virus challenge as well as to the age and antibody status of the host.^{23, 24} Interpretation of results in tests of immunity under these conditions, therefore, must consider these differences in the inoculum used as well as the criteria used to judge immunity.

Table 3 contains data from volunteer studies tabulated in a manner similar to Tables 1 and 2 but cases of illness without virus isolation are included. If the specific prechallenge level of antibody was determined and/or the rise in the convalescent serum was measured, the data are given. In general, fourfold rises in antibody titer were observed less frequently than in the natural infections, possibly because more of the volunteers had pre-existing serum antibodies. Subjects used as volunteers in most studies were young adults, usually 20 to 30 years of age. As was shown in Figure 2, most of them would be expected to have had demonstrable serum antibody against the different viruses before the experimental challenge.

Prechallenge antibodies against adenovirus and Coxsackie A-21 virus appeared to be quite protective both in preventing illness and against infection as indicated by virus isolation. Published data on the other enteric viruses and rhinoviruses are too scant to document efficacy but, from the data available, prechallenge antibody tends to make the volunteer resistant to infection.^{18, 46} In rechallenge studies with 2060-JH virus, the immunity was quite complete as shown in Figure 5.²²

Data obtained on parainfluenza type 3 infection in volunteers indicated little or no protection from prechallenge antibody at the levels observed. This is in contrast to the protection observed against parainfluenza type 3 infection in successive outbreaks of infection in Junior Village as noted previously.⁴ Data with regard to parainfluenza type 1 virus in volunteer experiments are similar in showing a poor protective effect from prechallenge antibody. It may be that for parainfluenza virus, the very large virus dose used in the volunteers is at fault rather than the inefficacy of antibody, or less likely, that immunity to natural infection may be transmitted through a mechanism unrelated to antibody. Full explanation of this discrepancy requires further experience.

Table 3. Specific Antibody Before and After Infection From Direct Challenge in Volunteers

VIRUS	TOTAL SUBJECTS	SUBJECTS WHO DEVELOPED COLDs		SUBJECTS FROM WHOM VIRUS WAS RECOVERED		SIGNIFICANT TITER OF PRECHALLENGE ANTIBODY FOR TABULATION	NUMBER OF SUBJECTS WITH FOURFOLD RISES OF ANTIBODY	REFERENCES
		Number with Pre-challenge Antibody	Total	Number with Pre-challenge Antibody	Total			
Respiratory Syneytial }	35	18	8	27	10	neut. > 32	18	31
	41	20	8	30	11	neut. > 32	NT	27
Parainfluenza 1	3	NT	NT	3	0	neut. > 4	1	51
	32	18	NT	24	NT	—	25§	40
Parainfluenza 3	2*	NT	NT	1	NT	—	2	51
	1	NT	NT	1	NT	—	1	1
	17†	9	8	10	9	neut. > 16	12	30
Rhinoviruses JH 2060-JH DC	21	NT	NT	6	3	neut. > 4	NT	49
	159	48	NT	9 (17)‡	NT	—	16 (71)‡	22
	10	4	0	6	2	neut. "K" > 0.5	3	48
Coxsackie A-21	30	12	4	24	11	neut. > 64	NT	44
Adenovirus type 1	11	2	0	4	0	neut. > 20	3	41
type 3	20	15	1	16	NT	neut. > 8	15	54
type 4	20	11	1	14	NT	neut. > 8	14	54
type 4	26	15	NT	NT	NT	—	17	13

neut. = reciprocal of highest dilution giving neutralization in tissue cultures.

NT, not tabulated.

* Inoculum was fifth monkey kidney tissue culture passage of the virus.

† A very large dose of virus was in the inoculum.

‡ Figures in parentheses represent the number of subjects tested for antibody before the challenge.

§ Rises in neutralizing complement fixing or hemagglutination inhibiting antibody.

	Pattern A	Pattern B	Pattern C	Pattern D	Colds	No Colds
First Challenge	●	●	○	○	17	38
Second Challenge	●	○	●	○	4	51
Number	2	15	2	36	● = Cold	
%	4%	27%	4%	65%	○ = No Cold	

Fig. 5. Patterns of immunity to rechallenge with 2060-JH virus in 55 volunteers.

In the case of respiratory syncytial virus there is so far only negative evidence with regard to any protective effect from the presence of prechallenge antibody, regardless of the titer. If this is in fact the case, the reasons remain to be elucidated.

INTERFERON

In the foregoing presentation no consideration has been given to interferon which may be important in determining the clinical course of virus infections.¹⁷ Interferon is a polypeptide which is elaborated by virus-infected cells and released into the surrounding intracellular spaces from which it enters nearby cells. This substance inhibits virus multiplication in those cells, and it is entirely independent of serum antibody in its mode of action. However, *in vivo* it may work intracellularly in concert with extracellular antibody to terminate a virus infection. In contrast to antibody, which affects the virus particle, interferon acts upon the metabolism of cells, and its action is limited to cells of the species by which it was produced. Therefore, it is unlikely to become readily available as a drug for therapeutic use in man.

PROSPECTS FOR A COMMON COLD VACCINE

Although some products referred to as common cold vaccines have been offered in past years, none has contained any of the common cold viruses nor has had a valid basis for the prevention of colds. With the recognition of specific viruses that cause cold-like syndromes, the techniques for their propagation in the laboratory, and the demonstration of immunity following infection, the essentials for the development of vaccines are achieved.

Our increased understanding of viral respiratory infections, however, has introduced new complexities. Evidence for the large number of viruses that cause the common cold and the specificity of the immune response has introduced problems of logistics in the administration of the number of vaccines necessary for protection, and raised new inquiry as to whether the game is worth the candle. The problem in new areas of discovery often seems insurmountable and such appears to be true in this area at present. It is quite certain that there will not be a "one-shot" common cold vaccine. On the other hand, it is likely that effective

vaccines can and will be made. The principal need in charting the course for vaccine development is recognition of the epidemiologically and pathogenically important strains of virus and the purification of the active antigenic components or the development of stable immunizing attenuated strains of live virus. Both courses offer good hope for the prevention of much morbidity and needless fatalities in selected high-risk populations; both will require patience and critical application before we will obtain the optimum benefit.

SUMMARY

The paradox of the lack of immunity in the common cold syndrome is reviewed in the light of the present knowledge of the multiple etiologies of the syndrome. Data are presented to show that common cold viruses stimulate specific serum antibody responses and that sufficient serum antibody will protect against infection. The concentration of antibody at the respiratory mucous membrane is postulated as a contributing factor in determining the course of the clinical illness. The immunity is shown to be transitory and incomplete, allowing reinfections to occur. These new infections stimulate further specific antibody formation and, depending on the interval, successive reinfections cause progressively milder illnesses.

The observed efficacy of antibody in persons who acquired infection after natural exposure to viruses is compared to its efficacy in persons challenged with viruses in volunteer experiments and the discrepancies which appear to exist are discussed. The protection against rechallenge with the same virus in volunteers correlates with the observation that natural illness from infection does confer immunity.

Interferon is described as a substance that might affect the course of respiratory virus infection. Vaccines against the common cold syndromes although not prepared at present will ultimately be available.

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Factors of Importance in the Control of Influenza

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INFLUENZA is the last uncontrolled great plague of mankind. Epidemics and pandemics of unpredictable size and severity recur with disturbing, though monotonous, regularity. Prevention can be achieved by vaccination, but the application of that procedure is still too limited to contain the national spread of epidemics.

APPROACHES TO CONTROLLING INFLUENZA BY VACCINATION (Selection of the Population to be Vaccinated)

Complete annual coverage of the entire population by vaccination against influenza would undoubtedly prevent the occurrence of epidemics as we now experience them. However, such an objective is currently unrealistic. Supplies of vaccine are limited and acceptance of vaccination against influenza is not uniform.

The question arises, then, how can we obtain the best results with the material at hand and the attitudes of the populations we work with?

The answers to that question vary, as does the scope of the objectives in mind. For maximal reduction in incidence, it would seem logical to utilize the available vaccine for the protection of that segment of the population which generally experiences the highest attack rate, namely children of primary and secondary school age. Moreover, since children of school age are the major source of introduction of respiratory infections into family units,⁹ other members of the household should acquire some benefit thereby. It has, of course, been clearly demonstrated that children in this age group can be protected by vaccination,^{7, 8} yet the question has not been answered whether vaccination of school children will significantly affect the spread of influenza among older segments of the population. Therefore the time seems ripe for setting up field experiments designed to supply an answer, since total national

A portion of the investigations reported was conducted under the auspices of the Commission on Influenza, Armed Forces Epidemiological Board, and was supported by the Office of the Surgeon General, U.S. Army, Washington, D.C.

coverage of school age children would present formidable problems in supply and administration of vaccine, and proof of efficacy is desirable prior to advocating the assignment of high priority for such a program.

For safeguarding the normal functioning of the community, certain critical services must be maintained. Hence, persons engaged in medical and health services, in public safety, public utilities, transportation, education and communications fields are urged to be vaccinated in years of expected high incidence.³ The success of vaccine programs oriented to such occupational groups recommends continuance of that procedure when an epidemic threatens.¹¹

There is a third objective which is more closely related to the practice of most physicians: the prevention of the influenza-associated deaths which in the past have been used as an indicator of the time of occurrence and the severity of outbreaks.^{1, 2} That such a marker can still be employed is a challenge to all of us, since there are cogent reasons to believe that such deaths are preventable.

Unfortunately, recurrent shortages in the supply of vaccine and periodic shifts in public interest often prohibit simultaneous efforts to meet each of these goals, i.e., to limit the incidence and spread of infection, to safeguard the community and to prevent deaths. At times, distressing decisions must be made concerning the use of the vaccine available. At present, the concept of voluntary allocation of vaccine in first priority for the prevention of influenza-associated death, as recommended by the Surgeon General's Advisory Committee on Influenza (U.S.P.H.S.),³ has received widest acceptance, and in this consideration will be given the major share of attention.

CAN INFLUENZA-ASSOCIATED DEATHS BE PREVENTED?

The thesis that the excess mortality which occurs during epidemics of influenza can be reduced by vaccination of appropriate patients rests upon two facts and one inference. The first is that vaccination affords a high degree of protection against influenza. The second is that the persons most likely to die during an epidemic of influenza can be categorized. The inference is that vaccination of persons at "high risk" will result in a lowering in the number of influenza-associated deaths. A brief comment on some features pertinent to each element of this hypothesis seems warranted.

The efficacy of influenza virus vaccines has been firmly established by the results of many field trials carried out in this country and abroad. The most extensive series of studies are those reported during the past two decades by members of the Commission on Influenza of the Armed Forces Epidemiological Board. The findings reviewed, or referred to, elsewhere^{5, 10} may be summarized as follows: The average degree of protection conferred by vaccination in 18 controlled field trials against influenza A, influenza A-prime, and Asian influenza, was 78 per cent. The range was from 41 to 90 per cent. Against influenza B and B-prime, the results of four field trials yielded an average protection of 90 per cent, with a range from 63 to 96 per cent. There was but one failure in

the 20 years' experience, and for reasons described in detail elsewhere⁴ it seems highly improbable that such a failure could recur without forewarning. Thus, today, influenza virus vaccines can be prescribed with full confidence that they will confer an important benefit.

It has been known for a long time that the burden of fatalities encountered during an epidemic of influenza is not distributed equally, but is clustered in certain easily identifiable segments of the population.^{1, 2} The report of Eickhoff et al.⁶ on the excess mortality associated with epidemics of Asian influenza re-emphasizes this point. Thus of the 86,000 excess deaths associated with the Asian influenza epidemics of 1957-1958 and 1960, 78,900 occurred in persons 45 or more years of age. The blight fell heaviest on persons aged 65 or older. Age alone, then, provides one criterion for recognition of high risk. Excess deaths numbering 43,900 occurred in persons suffering from cardiovascular-renal disorders. Likewise, excess mortality was observed in sundry other chronic disease states, e.g., asthma, diabetes mellitus, pulmonary tuberculosis and cirrhosis of the liver. The findings are in agreement with those of the classic studies of Collins and Lehman on mortality due to epidemic influenza.² From these, and from clinical and laboratory data on influenza-associated deaths (reviewed by Eickhoff et al.)⁶ the Surgeon General's Advisory Committee on Influenza (U.S.P.H.S.) attempted to define certain "high-risk" groups which should receive special emphasis in the campaign for better control of influenza.³ These are: (1) persons of all ages who suffer from chronic debilitating disease, e.g., chronic cardiovascular, pulmonary, renal or metabolic disorders; in particular, patients with (a) rheumatic heart disease, especially those with mitral stenosis, (b) other cardiovascular disorders such as arteriosclerotic heart disease and hypertension, especially those with evidence of frank or incipient cardiac insufficiency, (c) chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema and pulmonary tuberculosis, (d) diabetes mellitus, and (e) Addison's disease; (2) pregnant women; and (3) persons in older age groups; those over 45 and particularly those over 65 years of age.

One oft-voiced misconception, that influenza-associated deaths largely occur in persons of very limited life expectancy, deserves comment. If this were so, one would anticipate that in post-epidemic periods there would occur a considerable compensatory deficit in deaths among persons in the high-risk categories. The evidence demonstrates that only a very small deficit can be observed, even in years of very high incidence.⁶ Hence most victims of influenza epidemics are apparently not near-terminal patients in whom influenza is the final event, but on the contrary are individuals who might have lived considerably longer if they had escaped infection. In point of principle, preservation of life, without regard to extent, needs no defense. To recapitulate, the challenge to prevent these deaths remains with us until they no longer occur.

The inference that, if influenza is prevented by vaccination of persons at "high risk," the frequency of influenza-associated deaths will be reduced is based fundamentally on "prima facie" evidence. Prevention

of death of laboratory animals by vaccination prior to challenge with a lethal strain of influenza virus is a classroom exercise. Prevention of infection by vaccination of healthy subjects has been repeatedly demonstrated. Hence the supposition that prevention of disease will result in a decline in disease-associated deaths among "high-risk" patients seems most reasonable. Yet without formal proof of the validity of the inference, some doubts are occasionally expressed that vaccination can prevent influenza-associated deaths.

The counter hypothesis is that perhaps the degree of protection found in healthy persons may be less or inadequate when the chronically ill are vaccinated. There are no data to support this hypothesis, and neither proposition is ideal for direct testing since it would seem unacceptable to conduct a controlled field trial in which the efficacy of vaccination of the chronically ill was to be measured using death as an end point.

Since the arguments in favor of the concept that the influenza-associated deaths can be prevented by preventing influenza are far more persuasive than the reservations mentioned, adoption of a program for providing full coverage of the "high-risk" groups by vaccination would seem to comprise a logical basis on which to proceed in an attempt to control this aspect of the ravages of epidemic influenza. The merit of the crucial inference can be tested by observation, if the difficulties of full coverage of the "high-risk" groups can be resolved.

DIFFICULTIES IN PROVIDING FULL COVERAGE OF "HIGH-RISK" GROUPS

The mechanics of providing full coverage for "high-risk" groups in the population of the United States present formidable problems. From the data of the 1960 census and of the National Health Survey, one can obtain an approximation of the magnitude of this venture.*

Thus, in round numbers, there are probably about 48,983,000 persons in the United States who are 45 or more years of age and, of these, 14,513,000 are aged 65 or older. About 10,000,000 persons in the nation report a heart condition or high blood pressure. Similarly, 3,600,000 persons are listed as having asthma, 2,130,000 as suffering from chronic bronchitis, and 2,170,000 persons record the presence of other chronic respiratory disease. By like criteria, it may be estimated that there are at least 1,500,000 diabetics in our population and a conservative appraisal of the number of pregnancies per annum is 4,348,000. Approximately 1,550,000 persons suffer from nephritis or other diseases of the kidney. Of course these numbers cannot be summed to provide the overall dimensions of the problem we are considering. However, a conservative estimate would be that there are at least 50 million persons in the "high-risk" categories. This estimate is derived from the knowledge that there are 48,983,000 individuals in the population who are 45 or more years of

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age, and the assumption that the majority of the patients bearing the diagnoses listed would fall in this age group.

In relation to this estimate, one has to consider the amount of vaccine available for use. Under the stimulus of the excitement of the advent of Asian influenza, 50 million doses of vaccine were produced in 1957-1958. To meet the needs of the 1962-1963 respiratory disease season, 45 million doses were manufactured. In other years, the volume of vaccine produced has been considerably less. Hence, since even in years of peak production the total volume of vaccine available is not used exclusively for protection of the "high-risk" groups, we are faced with recurrent vaccine shortages if their requirements are to be satisfied.

In addition to problems in supply, there are equally vexing problems in administration of vaccine. Timing is of the utmost importance. The current recommendation is that vaccination be carried out as soon as practical after September 1. Persons who have received influenza virus vaccines in 1957 or since need only a single annual booster dose. For those not immunized during or since 1957 multiple doses are recommended, separated by various intervals according to age.³ The details of volume of vaccine, frequency of administration and intervals between doses by age and previous vaccine history are given in Table 1. The schedule of vaccinations should be completed by mid-December. However, if previously unvaccinated patients present themselves after October 15, they should be given their first dose promptly. A single dose is far better than none and may confer enough protection for many patients. The second or third dose, which adds an extra margin of certainty, can be given later if influenza has not already appeared locally. The only contraindication recognized is hypersensitivity to egg proteins.

Table 1. Recommended Dosage and Schedule for Inoculation

SUBJECT	PREVIOUSLY VACCINATED			NOT PREVIOUSLY VACCINATED		
	Volume	Frequency	Volume	Frequency	Interval	
Adult	1.0 ml.	Once	1.0 ml.	Twice	2 months	
Child aged 6 to 12	0.5 ml.	Once	0.5 ml.	Twice	2 months	
Child 3 months to pre-school age	0.1 ml. or 0.2 ml.	Once*	0.1 or 0.2 ml.	Three times	1 to 2 weeks* vs. 1st and 2nd dose; 2 months vs. 1st and last dose.	

Route: Subcutaneous.

Timing: Vaccination schedule to be completed by mid-December. Begin as soon as practical after September 1st.

Contraindications: Hypersensitivity to egg proteins.

* Acetylsalicylic acid (1 gr. per year of age) every 6 hours for first 24 advised to prevent or minimize febrile reaction in this age group.

Obviously, it is not easy to implement this program in office practice. Patients must be educated to accept immunization against influenza as a practical portion of the plan for conservation of their health. The physician, the patient and the vaccine must converge within a specified time period to obtain optimal results. Nevertheless, when the physician is faced with the knowledge that vaccination is the only proven method for preventing influenza, and the realization that influenza is a killer which has previously exacted its toll without restraint, the difficulties mentioned constitute a challenge rather than a deterrent to action. To remain passive in the face of this challenge is not in the tradition of American medicine.

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The Complications of Influenza

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MOST INDIVIDUALS during their lifetime will have experienced several episodes of illness due to influenza A and B viruses. Fortunately, the incidence of serious pulmonary, cardiovascular, neurologic and other complications from these common infections is very low in healthy persons. Nevertheless, considerable variation in frequency can be observed in different areas depending upon the socio-economic status and general health of the population. Other determinants include age of those afflicted and the presence of respiratory, cardiovascular, metabolic and other chronic diseases.^{4, 10, 14, 17} It is also possible that some epidemic strains possess more capabilities than others for causing complications, although this might, at least in part, be dependent upon the immune state of the population.³

PROPERTIES OF THE VIRUS THAT RELATE TO TISSUE DAMAGE

Influenza viruses exhibit toxic properties when injected into a variety of laboratory animals. An illness accompanied by a febrile reaction can be observed in these nonimmune hosts. Severity depends upon the amount inoculated and can lead to death. Pathologic changes consisting of engorgement of blood vessels and areas of necrosis are found in the tissues of these animals. This reaction is not due to multiplication of the virus and a somewhat analogous effect follows administration of influenza vaccine to man. Inflammation localized to the injection site occurs with a varying degree of fever depending upon the age and immune status of the individual. The virus does not appear to utilize this toxic effect for invasion of cells. A soluble antigen is also produced by multiplication of these viruses and antibody is found following infection of man. The role of this soluble antigen in disease has not been elucidated.^{4, 5, 6}

Capability for invasion of cells is probably dependent upon the virus enzyme, a neuraminidase, that splits nonspecific mucoprotein inhibitory

substances in body fluids. This enzyme contributes to attachment of the virus to host cells by its effect on receptor sites on the cell surface. Newly recovered strains are less reactive with inhibitory substances and probably have a greater affinity for cellular receptor sites of man than do viruses modified by growth in laboratory animals.^{2, 8, 13, 16}

Influenza viruses specifically invade and destroy ciliated epithelium of the respiratory tract. Cytopathic effects can also be demonstrated in cultures of kidney and lung from human fetuses and in monkey kidney. Evidence for multiplication of the virus in tissues other than the respiratory tract in the intact human is lacking. Nevertheless, strains can be adapted to growth in the lung, brain and vascular cells of laboratory animals. It is noteworthy that, prior to adaptation to the mouse lung, considerable virus multiplication takes place without producing pneumonia.^{2, 4, 12, 17}

Indications of variations in virulence of different strains of influenza viruses can be found by behavior in laboratory animals. Some cause death of embryonated eggs while others adapt more readily to growth in other laboratory hosts. In man, epidemics of influenza A seem to be associated with greater incidence of serious complications than those due to influenza B. This is more evident when a new variant appears in a nonimmune population.^{3, 4}

PATHOGENESIS

Influenza viruses are known to be transmitted only by the respiratory route. The ciliated epithelium of the nasal mucosa, trachea and bronchi is selectively invaded and focal areas of destruction are found during the second or third day of illness. Loss of cilia, pyknotic nuclei and disappearance of cell borders are followed by desquamation of superficial cells. The basal layer becomes flattened, and the latter constitutes the only epithelial lining after the second to fifth day. Afterward there is regeneration of undifferentiated epithelium without cilia or mucus production until the ninth to fifteenth day, at which time mucus production and cilia begin to appear again. Variations in degree of these changes are observed and most of the respiratory epithelium may be affected in some cases. Also, it is not clear whether there is involvement beyond the bronchi in uncomplicated influenza. Autopsy material reveals epithelial lesions in the bronchioles and alveolar cell linings accompanied by hyperemia, edema, hemorrhage or leukocytic infiltration of the tunica propria.^{7, 10, 17}

In the early stages of influenza virus pneumonia there is hyperemia and broadening of the alveolar walls with interstitial leukocytic infiltration, alveolar hemorrhage, and capillary thrombosis with increased focal leukocytic exudate, alveolar ducts and alveoli covered with exudate or hyaline membrane. In late stages epithelial proliferations are found in the respiratory bronchioles growing into adjacent alveoli and covering many alveoli. In the pathogenesis of pneumonia the first site of damage would be the alveolar cell lining and the vascular lesions might be secondary to the denuding of the alveolar walls or a consequence of viral infection of the endothelium.^{7, 10}

PULMONARY COMPLICATIONS

Probably the most common sequel of influenza is *tracheobronchitis*. Obviously, this should be expected because of the damage to the ciliated

epithelium. Even though the febrile stage of the illness has subsided in a week or less, reparative processes in the tracheobronchial tree require two weeks or longer. Bronchoscopic studies during the course of uncomplicated influenza A2 infection have shown epithelial necrosis 24 hours after the onset of clinical symptoms. Loss of epithelial cells, metaplasia, thickening and hyalinization of the basement membrane, and inflammatory reaction in the tunica propria were constant features in these biopsy specimens. Thus, it is not surprising that secondary bacterial infection is a common complication of this tracheobronchitis. If antibiotics have not been administered prematurely, pneumococci, staphylococci, *Hemophilus influenzae*, and sometimes other organisms will be found as the infecting agents. Accordingly, Gram-stained sputum smears must be examined at frequent intervals and cultures taken whenever a productive cough follows an episode of influenza. In addition to preventing pneumonia, illness may be shortened by appropriate therapy especially in persons with bronchiectasis, emphysema or other chronic pulmonary diseases.¹⁹

Bacterial pneumonia that has its onset early in the course of influenza may pursue a fulminating and dangerous course. This type of pneumonia might represent a combination of viral and bacterial infection in which rapid invasion and spread is made possible by the preceding viral injury to bronchioles and alveoli with resulting hyperemia, edema and exudate. Delay in recognition of onset of this serious complication frequently occurs because a febrile illness is already present. Increased dyspnea and productive cough are indications of onset of pneumonia. Unfortunately, many persons wait until the next day to seek medical attention. Extensive bilateral pneumonia may then be present and death can occur within six hours despite vigorous therapy. Appropriate antibiotics, adrenal corticosteroids, oxygen, intermittent positive pressure respiration, and even tracheotomy for removal of excessive secretions are measures that might maintain respiratory exchange during the critical phase. Those patients who respond to therapy of the bacterial infection may have a prolonged recovery period because of the residual pulmonary damage from the virus component of the disease.^{7, 14, 17}

Pneumonias that occur near the end of the febrile phase or shortly thereafter usually are not difficult therapeutic problems unless there is predisposing chest disease, complicating chronic illness or an antibiotic-resistant organism as the etiologic agent. Early recognition, accurate bacteriologic diagnosis and appropriate therapy are obviously important, especially when caused by the staphylococcus. The latter causes necrosis of the basal cell layer and destruction of the basement membrane. Recovery after delayed or inadequate therapy may be complicated by permanent alterations, consisting of obliteration of the elastic fibers and fibrosis of the tunica propria with hyalinization and distention of the basement membrane, which can result in bronchiectasis. A purulent sputum mixed with blood is often an early indication of the development of staphylococcal pneumonia.

Primary influenza virus pneumonia may occur at any age or condition of health, but it is probably more common or, at least, more likely to be

fatal, in persons with heart disease, especially mitral stenosis. These individuals are seriously ill with extreme dyspnea and cyanosis. There are scattered rales and inspiratory wheezes and coarse breath sounds without a definite area of consolidation. Roentgenograms of the chest reveal a fanning perihilar infiltrate of a diffuse and nodular nature. Therapeutic problems include progressive respiratory distress, hypoxia and respiratory and metabolic acidosis. Intermittent positive pressure breathing and, possibly, adrenal corticosteroids are helpful therapeutic measures. Antibiotics should be administered to these individuals because it is difficult to exclude the possibility of a combined virus and bacterial pneumonia. At autopsy, considerable quantities of virus can be recovered from the lungs, but evidence of bacterial infection will not be found. Mortality rates are very high in persons with heart disease complicated by primary influenza virus pneumonia. It seems likely that pulmonary hypertension associated with mitral stenosis plays a role in the pathogenesis of this hemorrhagic, edematous pneumonia.¹¹

PREVENTION of the pulmonary complications of influenza is best done by annual vaccination of individuals with chest or heart disease. The use of pooled human gamma globulin has not been explored and probably would be unpredictable because of variation in amounts of specific antibody. Avoiding administration of antibiotics in uncomplicated influenza may not reduce the number of bacterial infections, but it will prevent invasion by organisms that are more difficult to treat. Early diagnosis is the most effective means of preventing serious complications. Frequent examinations of the chest with roentgenograms as needed and careful attention to the development of chest pain, dyspnea or productive cough are essential. Stained smears and cultures of sputum on a daily basis will frequently provide evidence of bacterial invasion prior to the onset of pneumonitis. Obviously, bed rest for all persons with influenza is mandatory. The home environment is usually safer than that of the hospital because the individual is not exposed to a dangerous bacterial population and, in turn, he will not infect patients with other illnesses.

CARDIOVASCULAR COMPLICATIONS

Influenza, like other acute infectious diseases associated with fever and toxicity, produces effects on the cardiovascular system that can be observed and measured.

Cyanosis, bradycardia or tachycardia, arrhythmias and hypotension may be found in cases without previously known cardiovascular disease. *Digital plethysmography* during the height of illness exhibits decreased digital blood flow as evidenced by the time course curves of volume, rate and acceleration in rates of inflow, outflow, and differences between inflow and outflow. Increased blood flow accompanies improvement and normal patterns are present upon full recovery. *Electrocardiograms* reveal temporary alterations in T waves. The latter may be inverted, diphasic, lowered or iso-electric in one or more leads. These manifestations are usually more prominent in precordial leads V₄ through V₆, although in many the standard leads exhibit similar changes. Other alterations

are observed in occasional subjects. Effect on the electrocardiogram is most obvious early in the illness and usually disappears with convalescence. *Spatial vectorcardiograms* reveal aberrations or irregularities in contour of the QRS S \bar{E} -loop. These may reflect alterations in depolarization, produced by subtle injury, which are not detectable in the conventionally recorded electrocardiogram. These distortions usually disappear with convalescence.^{1, 18}

It is not surprising that an infection such as influenza, that causes considerable damage to the respiratory epithelium, toxicity, and probably decrease in pulmonary blood flow, should be extremely dangerous to persons with pre-existing heart disease. Undoubtedly the degree of spread, from nasal epithelium to trachea and bronchi and from there to bronchioles and alveoli with development of pneumonia, determines the additional load on the cardiovascular system. Bacterial infection in the form of bronchitis or pneumonia can increase this burden. As a result of influenza there were 86,000 excess deaths during the period from 1957 to 1960 in the United States. More than half of these were persons with cardiovascular-renal disease, and over two-thirds of the total were in those who were 65 years of age and older. This represented a transition since the 1918-1919 epidemic, when 92 per cent of the excess was due to influenza and pneumonia. During the past 10 to 15 years only a fourth of the deaths have been due to this cause. Obviously, prevention of influenza by immunization is very important to the patient with cardiac disease. When the illness occurs in nonimmune individuals, immediate bed rest and careful observation for cardiovascular or pulmonary involvement are necessary for management of each problem as soon as it appears. It would also be very prudent to extend the period of convalescence for several days beyond the febrile stage of all patients with any type of cardiovascular disorder.¹⁰

Myocarditis as a clinical entity is a rare complication of influenza, occurring during or a few days after the febrile illness. Many reports have described cellular infiltrations, necrotic foci or generalized degenerative changes in heart muscle. Occasionally virus has been recovered, presumably from the myocardium. Even though adequate laboratory evidence of influenza virus infection may be obtained, this does not exclude the presence of another infectious agent. In an epidemic chance might associate influenza with other diseases. Growth of virus in myocardial cells in man, laboratory animals or heart muscle tissue cultures has not been observed. Nevertheless, this does not exclude the possibility of a toxic myocarditis since heart muscle cells are affected in the same fashion as other cells by the toxic action of influenza viruses in tissue culture. *Pericarditis* and *endocarditis* have also been described as unusual complications. It is more probable that the virus would have the capacity to multiply in endothelium than in muscle cells. There is evidence that neurotropic strains invade the small blood vessels before the nerve cells. This would presuppose a viremia, but the latter has not yet been found in man. Also, the virus would then be exposed to non-specific neutralizing substances in the blood.^{9, 16, 17}

Thus, primary action of influenza viruses on the heart or blood vessels of man has not been clearly established. However, effects, whether primary or secondary, are sufficiently frequent to warrant care. The

phenomenon of sudden death, presumably due to myocarditis in an apparently healthy individual, is a rare but very distressing happening during or shortly after illness. Bed rest throughout the disease and for a couple of days thereafter might make these cardiac complications less severe and prevent fatalities.

NEUROLOGIC COMPLICATIONS

Toxic effects of influenza viruses are best demonstrated by intra-cerebral injection of mice. Although unadapted virus does not multiply with production of more infectious particles in this tissue, there is invasion of cells with formation of aberrant or incomplete forms. Evidence favors separation of the toxic property from infectivity but, even with inactivated virus, toxicity can be shown. Proof is not absolute that this effect is completely different from viral multiplication. At any rate, it is theoretically possible for influenza virus to affect the central nervous system of man by similar mechanisms provided that infectious virus or its toxic form or products thereof are capable of reaching this tissue. Also, strains of influenza viruses have been adapted to growth in mouse brain with production of a hemorrhagic encephalitis. Here, the major damage is to small blood vessels. Either of these mechanisms could explain the central nervous system manifestations that are observed in varying degrees in persons with influenza. Of course, natural adaptation of virus to the brain could conceivably occur without an opportunity for spread of such a potentially dangerous agent to other individuals.^{5, 10}

One of the problems of evaluating nervous system disorders that occur during or shortly after influenza is that of determining relationship. Obviously, a disease that can affect a large proportion of the population at one time will be associated by chance with many and various illnesses. This was especially manifest by the frequent occurrence of encephalitis lethargica following the 1918 pandemic, but the relationship to influenza has never been clearly established. Nevertheless, there have been sufficient observations since then and including the years of influenza A2 to warrant description of three types of neurologic complications, a toxic encephalopathy, a virus encephalitis, and a postinfluenza demyelinating disease. Unfortunately, like the problems of cardiovascular complications of influenza, there has been no definitive method of demonstrating the association of virus infection with neurologic disease. Also, there have been no reports of viruses recovered from man that exhibited cardiotropic or neurotropic properties in animals. The occasional description of virus isolated from cerebrospinal fluid or brain tissue might have been due to contamination of autopsy material. Nevertheless, some of these cases have had typical tracheal and pulmonary lesions of influenza.^{10, 17}

Toxic encephalopathy may cause delirium, acute psychotic episodes, or coma. Electroencephalographic abnormalities have also been demonstrated in these individuals. Fatal cases have also occurred in which delirium, convulsions and coma are accompanied by pleocytosis in the

cerebrospinal fluid. Hemorrhagic encephalitis or other manifestations of virus encephalitis are observed in these at autopsy. Postinfluenzal demyelinating disease is probably like that following any acute infection or vaccination. Polyneuritis, encephalitis, myelitis and the Guillain-Barré syndrome may be observed with sufficient frequency during convalescence from influenza to strongly suggest a causative relationship. This, of course, implies a greater incidence of these illnesses in association with epidemics.¹⁰

Other than prevention of influenza there are no obvious means of avoiding neurologic complications. The administration of adrenal corticosteroids may contribute to the therapy of postinfectious demyelinating disease, but this has not been definitely established. It may not be prudent, however, to follow the same course when active virus multiplication is causing illness of the central nervous system. Even here, however, all measures including tracheotomy and use of a respirator should be considered when heroic therapy is needed.

OTHER COMPLICATIONS, INCLUDING THE COMMUNITY

A relatively frequent ailment for which a mechanism has not been delineated is that of *postinfluenzal asthenia*. This state of general ill feeling may last a few weeks but it is not totally incapacitating, nor have there been indications that more serious consequences ensue. It has been postulated that this complication might be due either to depletion of the adrenal cortex, to emotional or personality factors, or to a reaction from the generalized toxicity of the virus on a slowly replaced metabolic substance. Measures for prevention or therapy of this complication have not been developed.

The impact of influenza on a modern sophisticated society can be readily seen by the increase in use of antibiotics. This is only partly due to abuse of these drugs because bacterial infections are common complications. Included are purulent bronchitis, pneumonia, sinusitis, otitis media and diseases secondary to these such as empyema, lung abscess, brain abscess and meningitis. In addition to the individual the entire population can become involved by a Group A streptococcal outbreak following in the wake of an influenza epidemic. Although this relationship might be circumstantial, it has occurred frequently enough to strongly suggest a direct effect on acquisition of infection and spread of streptococci.¹⁰

The community can become involved in a more immediate fashion by an explosive epidemic of influenza in which personnel of essential utilities become ill simultaneously. Medical facilities can also be similarly affected and this will be compounded by increase in patient admissions and spread of infection to those already hospitalized. The significance of epidemic disease on military strength is well known to all students of history. Thus, it is imperative that persons who are essential to the functions of a community as well as those with chronic illnesses should be immunized annually.

GENERAL PRINCIPLES OF PREVENTION AND MANAGEMENT

Except by immunization there are no effective means of preventing infection by influenza viruses nor ways of determining in advance whether the predicted illness will be asymptomatic, mild or severe. Excess mortality data have shown that certain groups experience most of the complications. Included are persons with chronic cardiovascular, pulmonary, renal or metabolic disorders, those over 60 years of age and pregnant women. Immediate bed rest, preferably at home, with frequent observations by the physician, followed by several additional days of inactivity after the acute stage, regardless of its severity, should be fundamental procedures. A throat culture at onset and daily smears and cultures of sputum if productive cough is present will contribute much to prevention of pneumonia by indicating the need for therapy of bacterial infection of the bronchi. Vigorous therapy with the appropriate antibiotic and, if severe pneumonia develops, positive pressure respiration and even adrenal corticosteroids and tracheotomy should be used to maintain life. Careful attention to examination of the heart will provide more instances of diagnosis of these problems in the early stages and allow time for therapeutic measures to be effective. In general, recognition of the rapidity of development and spread of influenza and the increased rate of onset of complications would do much to reduce the mortality. Analysis of individual fatal cases frequently will reveal that there was delay in therapy. Often this has been caused by the patient who did not realize the seriousness of his disease, but the same error in timing has frequently been caused by the physician.

SUMMARY

The pathogenesis and clinical features of the major pulmonary, cardiovascular and neurologic complications of influenza have been discussed. Although prevention of the disease would be preferable, adequate therapeutic measures can reduce the excess mortality caused by this common infection. Awareness by the public and the physician of the dangers of these rapidly developing serious complications is fundamental to effective therapy.

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The Etiology and Therapy of Atypical Pneumonia

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AT ONE TIME, pneumonia lacking the classical clinical, laboratory and roentgenologic features of infection produced by *Diplococcus pneumoniae* was termed "atypical pneumonia." The etiology of certain cases of "atypical pneumonia" was clarified by the discovery of the influenza and psittacosis viruses; cases in which no etiologic agent could be identified, and in which cold hemagglutinins were often demonstrable, were called "primary atypical pneumonia." The nomenclature of the pneumonias has become increasingly confusing during the past decade because of the discovery of many new infectious agents, insight into the nature of previously described agents, and the development of specialized diagnostic procedures. It is now clear that all classes of micro-organisms which infect man may produce "atypical" forms of pneumonia, and currently it is possible to associate specific agents with at least half of these infections.

This discussion will attempt to outline current concepts of the etiology and therapy of the atypical pneumonia syndrome. Special attention will be given to Eaton's atypical pneumonia agent, since this micro-organism is the leading known cause of the syndrome. Recent information indicates that Eaton's agent belongs to the genus *Mycoplasma* (pleuropneumonia-like organisms, or "PPLO"). The *Mycoplasmataceae* have been of importance formerly only to the veterinarian and the research microbiologist; they now become of importance to the physician as well, in that the knowledge that Eaton's agent is a PPLO clearly links this genus of micro-organisms to human disease for the first time. Etiologic distinction of the pneumonias is essential, since specific therapy is now available for disease due

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COLD AGGLUTININS ABSENT		COLD AGGLUTININS PRESENT*	
MYCOBACTERIA:	Tuberculosis		↔ ?
BACTERIA:	Pneumococci <i>H. influenzae</i> Staphylococci		
FUNGI:	Histoplasma Blastomyces Coccidioides		
RICKETTSIA:	Q Fever	MYCOPLASMA:	Eaton PPLO
PROTOZOA:	<i>Pneumocystis Carinii</i>		
VIRUSES:	Psittacosis Influenza Parainfluenza ECHO Coxsackie Respiratory Syncytial Adenovirus		
		↔	

* This group has been called "primary atypical pneumonia".

Fig. 1. Etiology of the atypical pneumonias.

to bacteria, mycobacteria, fungi, rickettsia, psittacosis virus, and Eaton's PPLO.

ETIOLOGIC CONSIDERATIONS

General

Atypical pneumonia may be produced by infections with mycobacteria, bacteria, fungi, rickettsia, protozoa, mycoplasma and viruses. Prominent members of these groups of organisms associated with the atypical pneumonia syndrome are outlined in Figure 1. Consideration of all these infections would be virtually a review of the field of clinical microbiology, and is beyond the scope of this paper. Infection with *M. tuberculosis* may at times produce an "atypical" pneumonia. Among the bacteria, pneumococci, *Hemophilus influenzae* and staphylococci can produce the syndrome. Certain fungi—notably histoplasma, blastomyces and coccidioides—may cause an identical clinical picture, as can the rickettsia of Q fever and the psittacosis and influenza viruses.¹⁴ More recently recognized as the cause of an unusual type of pneumonia is the protozoan, *Pneumocystis carinii*.¹

Twenty years ago exclusion of infection with the agents listed thus far would have provided sufficient criteria for a diagnosis of "primary atypical pneumonia." Further subdivision of the cases was impossible until the demonstration in 1943⁴⁰ that certain patients developed agglutinins reactive against human erythrocytes in the cold. In addition to the organisms listed above, a variety of other agents have been found to produce pneumonia which is *not* associated with the development of cold hemagglutinins: these include the adenoviruses and the parainfluenza,

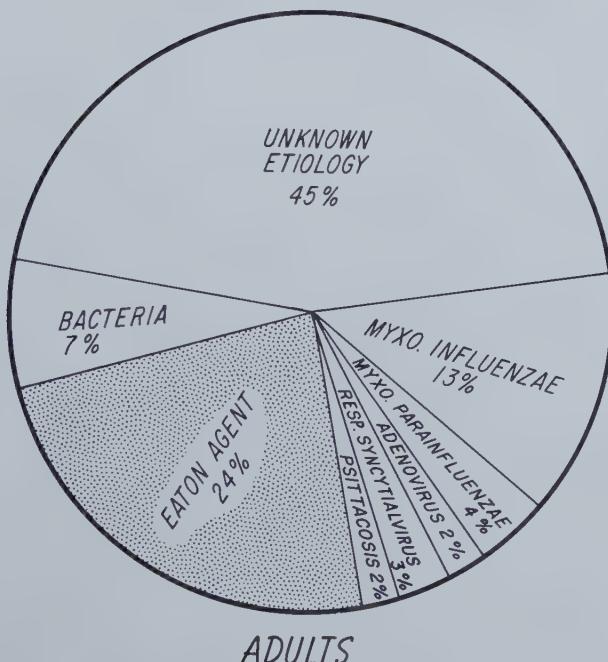
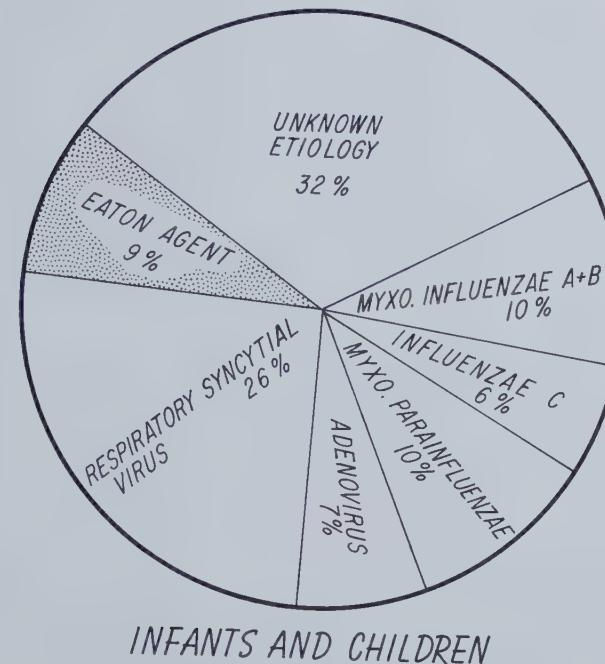


Fig. 2. Estimates of the relative position of identifiable agents in respiratory disease of children and adults requiring hospitalization. (Adapted from Hilleman et al., J.A.M.A. 180: 445, 1962.)

ECHO, Coxsackie and respiratory syncytial viruses. Pneumonia in which cold hemagglutinins develop has been associated with only one agent, a PPLO which was first isolated by Eaton in 1944.¹⁶

In many of the earlier reviews on the subject of atypical pneumonia, information on the etiology of the cases could not be obtained because suitable techniques were not available. Knowledge of the microbiologic aspects of pneumonia now makes possible specific diagnoses in the majority of cases, as indicated in Figure 2; it is also possible to estimate the relative roles of the identifiable respiratory disease agents.²⁸ In children, a large segment of pneumonia is produced by the respiratory syncytial virus, with adenoviruses, influenza and parainfluenza viruses, and Eaton's agent making relatively minor contributions (Fig. 2, upper). In adults, Eaton's agent assumes much greater importance, and may account for about one-fourth of all cases of pneumonia (Fig. 2, lower). Here the relatively minor roles of both bacteria and viruses are noteworthy. The prominent position of Eaton's agent in causing pneumonia, especially in adults, makes detailed consideration of this peculiar organism appropriate.

Eaton's Atypical Pneumonia Agent

HISTORICAL RESUMÉ. In 1944, Eaton and co-workers reported the isolation of an infectious agent from certain patients with atypical pneumonia which could induce pneumonia in cotton rats.¹⁶ This agent was found to be "filterable," and thus was assumed to be viral in nature. Later studies indicated that the agent was thermostable and had a very limited experimental host range, making it technically difficult to handle in the laboratory.¹⁷ While Eaton's group was able to relate the agent to atypical pneumonia through repeated isolations and demonstration of the development of neutralizing antibodies,¹⁸ confirmation of their findings by other workers was not immediately obtained.

During World War II management of atypical pneumonia in recruits posed a serious problem for the armed forces, and the Commission on Acute Respiratory Diseases of the Armed Forces Epidemiological Board performed a series of experiments for investigation of this problem.¹² Using bacteria-free filtrates of sputa and throat washings from clinically characteristic cases, it was determined that the pneumonia was transmissible to volunteers. The chief relationship between these cases of experimental pneumonia and the patients studied by Eaton was the appearance of cold hemagglutinins in many of the subjects. Since cold hemagglutination is known to be a nonspecific phenomenon, no etiologic significance could be attached to this relationship at the time.

In 1957, Liu described a technique which provided greater facility in making serologic diagnoses of Eaton agent infections.³¹ Eaton had shown earlier that the agent multiplied in chick embryos, but no pathology was produced. Liu localized the antigen of the agent to the chick embryo bronchial epithelium by applying the fluorescent antibody technique, thereby providing a system which could be used to indicate the presence of antibody in unknown sera. These "fluorescent-stainable antibodies" have been sought extensively in studies of the occurrence and epidemiology of Eaton agent infections. Application of Liu's methods was made by Cook et al.¹³ and by Evans and Brobst²⁴ to indicate the great frequency of Eaton agent disease in various population groups.

In 1961, Clyde, Denny and Dingle⁷ studied retrospectively sera which had been preserved from the atypical pneumonia experiments of the Commission on Acute Respiratory Diseases. Using Liu's techniques, they demonstrated that

Eaton's agent had been involved in these experiments. Significant fluorescent-stainable antibody responses occurred in those men receiving infectious inocula who developed pneumonia, as well as in those experiencing mild or subclinical infections. This spectrum of disease due to Eaton's agent has also been demonstrated in studies of military recruits by Chanock and co-workers.² These investigators established through epidemiologic and serologic data that only about one Eaton agent infection in 30 was characterized by clinically diagnosable pneumonia.

The most recent chapter in the history of Eaton agent infections has been written at the National Institutes of Health. Koch's postulates were fulfilled by Chanock³ and Rifkind⁴ and their co-workers, who recovered the agent from patients, propagated it in the laboratory, reproduced the disease by inoculation of volunteers, and again recovered the organisms. The association of the agent with human disease described first by Eaton has thus been conclusively established.

THE NATURE OF EATON'S AGENT. Early assumptions that Eaton's agent was a virus stemmed from several facts. Eaton's studies indicated that the infectious particle was about $200\text{ m}\mu$ in diameter,¹⁷ which is slightly smaller than a vaccinia virus particle, and the agent was thus "filterable" as opposed to the bacteria. Application of the commonly-used histopathologic techniques to infected animal tissues failed to reveal the nature of the agent, nor had evidence of the infecting agent been demonstrated in autopsy material from rare fatal cases of atypical pneumonia.³⁸ Donald and Liu were unable to clarify the nature of Eaton's agent by studying sections of infected chick embryos known to contain the fluorescent-stainable antigen.¹⁵

In 1961, Marimon and Goodburn produced the first direct evidence that Eaton's agent was not a virus.³³ Using an intensified Giemsa staining technique, they found minute coccobacilli lining the bronchi of infected chick embryos, which corresponded to the areas containing fluorescent-stainable antigens. Similar techniques were applied by Clyde to tissue cultures infected with Eaton's agent.⁸ After Giemsa staining, extracellular microcolonies of minute cocci were found in inoculated cultures. The colonies could be specifically identified by means of fluorescent antibody. These data suggested that the agent was a pleuropneumonia-like organism; that this is the case was established in 1962, when Chanock, Hayflick and Barile successfully cultivated the organisms in artificial media.⁴

The identification of Eaton's agent as a PPLO has revolutionized the problem of making etiologic diagnoses in cases of atypical pneumonia. Techniques currently available are adaptable to use in the clinical microbiology laboratory, providing a more prospective diagnosis than is possible with reliance upon serologic responses. The implications of these findings can best be understood with some knowledge of the biologic properties of Eaton's organism.

PROPERTIES OF EATON'S PPLO. Various properties of the PPLO generally and of Eaton's PPLO specifically are outlined in Table 1. In size, individual organisms are about one-fourth the diameter of a single streptococcus. Colony size is variable, but seldom exceeds 0.5

Table 1

PROPERTIES OF THE PLEUROPNEUMONIA-LIKE ORGANISMS (PPLO)

1. Size	150-300 m μ diameter.
2. Shape	Variable. Lack rigid cell wall.
3. Colonies	Less than 0.5 mm. diameter. Grow into the agar, as well as on surface.
4. Growth	Fastidious. Require sterol.
5. Effect of antibiotics	Absolute resistance to penicillin.
6. Effect of antiserum	Inhibited by specific antibody in the absence of complement.

PROPERTIES OF EATON'S PPLO

1. Size	180-220 m μ diameter (filtration).
2. Shape	Minute cocci or coccobacilli.
3. Colonies	10-50 μ diameter. Appear usually as small spheres, half-submerged in the agar.
4. Growth	Require specially prepared yeast extract, and serum. Grow well aerobically. Can be cultivated in chick embryo by amniotic inoculation. Produces pneumonia in cotton rats and hamsters. Grows in a variety of tissue cultures.
5. Effect of antibiotics	Resistant to penicillin, bacitracin, polymyxin B. Sensitive to oleandomycin, tetracycline, tetracycline derivatives.
6. Effect of antiserum	Growth inhibited in presence of specific antiserum, or sera from patients convalescing from atypical pneumonia.

mm.; a microscope or hand lens must be used to visualize the colonies. PPLO colonies differ from bacterial colonies in that they grow into the agar surface, and cannot be picked up with a bacteriological loop. Colonies thus appear as spheres, half-submerged in the agar, or as "fried eggs" if there is an element of surface growth on the agar around the thicker central part of the colony. The appearance of colonies of Eaton's PPLO growing on a transparent agar medium is shown in Figure 3.

PPLO differ structurally from bacteria in that they lack a rigid cell wall. This renders them more pleomorphic and more fragile than bacteria, and explains their characteristic of resistance to penicillin. The PPLO, including Eaton's organism, are variably sensitive to the action of the tetracycline family of antibiotics.

Most PPLO are fastidious in their nutritional requirements, requiring special media for growth. The original medium used for cultivation of Eaton's PPLO contained a beef heart infusion and proteose-peptone base, supplemented with horse serum and freshly prepared yeast extract. Eaton's PPLO grows slowly on this medium, and colonies may not be evident for five to ten days after inoculation of the agar. Definition of various factors stimulating growth may foster more rapid diagnosis by recovery of the organisms in the future.

As is the case with other PPLO, growth of Eaton's organism can be inhibited by specific antisera. Eaton first demonstrated this effect in 1945 by showing that cotton rats were protected from induction of pneumonia when sera of patients convalescing from atypical pneumonia were mixed with the inocula.¹⁸ More recently, a similar effect has been

Fig. 3

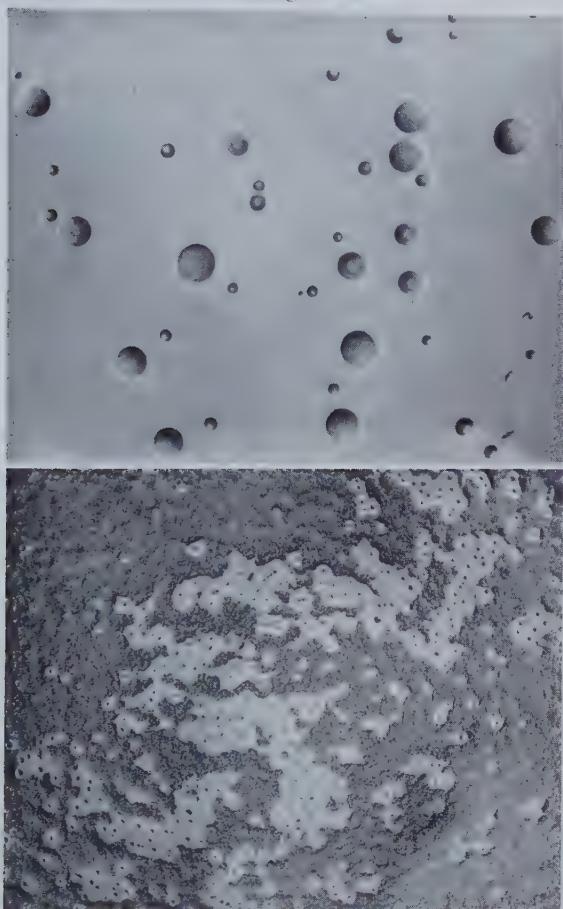


Fig. 4

Fig. 3. Colonies of Eaton's PPLO on transparent agar medium. Colony diameter varies from 10 to 100 μ . $\times 400$.

Fig. 4. Appearance of a week-old culture of Eaton's PPLO 24 hours after addition of a sheep blood agar overlay. Zones of clear hemolysis surround individual colonies, and coalesce to form larger areas where colonies are closely spaced. $\times 50$.

shown in neutralization of infectivity of Eaton's PPLO in tissue cultures by the presence of immune sera.^{11, 23}

At least three PPLO, *M. hominis* types 1 and 2, and *M. salivarium*, may inhabit the mouth and pharynx of normal adults.³⁶ These strains grow on media suitable for recovery of Eaton's PPLO, and may be confusing in evaluation of cultures from patients with pneumonia. Several biologic properties are helpful in distinguishing these particular PPLO strains, as shown in Table 2. Eaton's PPLO grows more slowly on agar than the other strains; the colonies are smaller, and are usually spherical as opposed to the "fried egg" morphology of the *hominis* and

Table 2. Differential Biologic Properties of Four PPLO Strains Isolated from Man

PROPERTIES	PPLO STRAINS		
	M. hominis I + II	M. salivarium	Eaton's PPLO
Growth on agar:			
Rate.....	Rapid (1-2 days)	Rapid (2 days)	Slow (5-10 days)
Colony:			
Size.....	> 100 μ	> 100 μ	< 100 μ
Morphology.....	"Fried egg"	"Fried egg"	Spherical
Anaerobe.....	No	Yes	No*
Growth in broth:			
Turbidity.....	Faint, diffuse	Diffuse	Granular
Surface "scum".....	Absent	Present	Absent
Hemolysis†.....	Absent	Absent	Present

* Growth enhanced by 5 per cent CO₂ in air.

† Mammalian erythrocytes.

salivarium strains. In liquid media, Eaton's PPLO produces a finely granular turbidity, while the other strains produce a homogenous turbidity. *M. salivarium* is distinguished by formation of a "scum" on the broth surface after 10 to 14 days' incubation; this strain also requires anaerobic conditions for optimal growth.

Eaton's PPLO has one biologic property which is not shared by other PPLO that have been recovered from man: this is an ability of the organisms to lyse mammalian erythrocytes. The hemolytic capacity of PPLO colonies is easily evaluated by pouring a blood agar overlay onto culture plates bearing mature colonies.¹⁰ Several species of mammalian erythrocytes are suitable for this purpose, although sheep or guinea pig bloods are superior. Eaton's PPLO colonies produce beta hemolysis in the blood agar overlay after about 24 hours (Fig. 4). The other strains mentioned either produce no hemolysis, or faint alpha hemolysis may occur after several days. This property permits tentative identification of Eaton's organism, since the other known PPLO of human origin do not possess similar hemolytic ability. The technique described can be applied to initial cultures from patients, providing a rapid and simple means of distinguishing Eaton's PPLO.

SEROLOGIC REACTIONS IN EATON PPLO INFECTIONS. For many years, the only useful serologic tests for atypical pneumonia were measurement of cold hemagglutinins and streptococcus MG agglutinins.⁴³ Both of these antibodies are nonspecific, and develop in many patients convalescent from atypical pneumonia, along with false-positive Kahn reactions and complement-fixing antibodies for a variety of heterologous antigens.¹⁴ In addition to these nonspecific responses, other serologic reactions thought to be related definitively to Eaton PPLO infections have

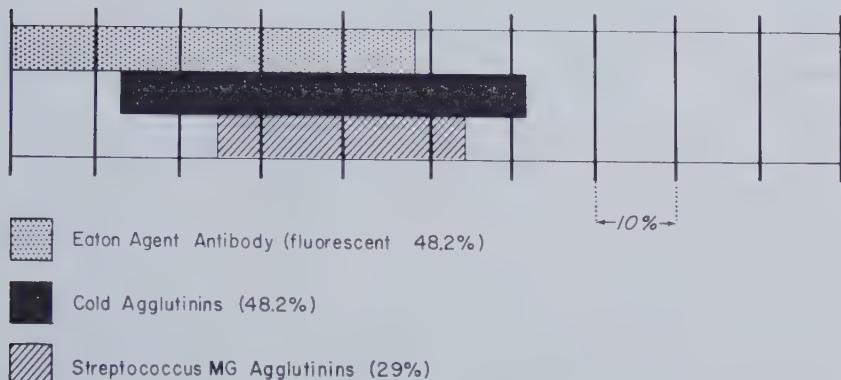
OCCURRENCE OF 3 ANTIBODIES DEVELOPING IN 112 PATIENTS
WITH ATYPICAL PNEUMONIA (Cleveland, 1947-1949)

Fig. 5. The relationship of specific Eaton agent antibody and 2 non-specific antibodies is indicated by overlap of the bars. The space between adjacent vertical lines represents 10 per cent of the cases.

been described: these include development of neutralizing and fluorescent-stainable antibodies, and possibly complement-fixing antibodies against specific antigen.

Cold Hemagglutinins. The cold hemagglutination technique is readily available in most clinical laboratories, and would thus seem to offer an expedient means for diagnosis of Eaton PPLO infections. Unfortunately, the degree of response is directly related to the severity of the patient's disease,⁷ and milder illnesses due to Eaton's PPLO may not be accompanied by development of this antibody. Therapy used may also influence the degree of response.²⁵ While occasional patients develop cold hemagglutinins during the first week of illness, the peak is not reached usually until the second or third week, making this test more valuable in retrospective than in prospective diagnosis.

Not all patients with Eaton PPLO infections develop cold hemagglutinins, and some patients with this response do not show evidence of Eaton PPLO disease. This relationship is illustrated in Figure 1 and in Figure 5. Whether PPLO other than Eaton's organism can cause pneumonia associated with the development of cold hemagglutinins is a matter of speculation at present.

Streptococcus MG Agglutinins. Agglutinins for the MG strain of nonhemolytic streptococci have been reported less frequently in atypical pneumonia than have cold hemagglutinins.⁹ The test is more difficult to perform, and contributes little additional diagnostic information in most instances. This antibody is often found in patients who also develop cold hemagglutinins and antibodies for Eaton's PPLO, as indicated in Figure 5.

Neutralizing Antibody for Eaton's PPLO. Convalescent-phase sera from many patients with Eaton PPLO infections have the ability to inhibit growth of the organisms.^{11, 18, 23} The procedure is less sensitive than other specific tests now available, and the techniques are not readily adaptable to the diagnostic laboratory.

Flourescent-Stainable Antibody for Eaton's PPLO. Antibody measurable by the methods of Liu (see Historical Resumé above) has been widely employed in many of the studies providing current information on Eaton PPLO infections.

This test appears to be quite sensitive and specific, offering a sound means of retrospective diagnosis. The techniques are not adaptable to use in the average clinical diagnostic laboratory, however.

The relationship of this specific antibody response and the nonspecific responses has been indicated above (see Figure 5). Patients developing cold hemagglutinins are estimated to have fluorescent-stainable antibodies for Eaton's PPLO in 50 to 80 per cent of cases.^{2, 13, 24, 32} While no exact figure can be derived currently, these specific antibodies often occur in the absence of cold hemagglutinin rises. Fluorescent-stainable antibody responses are unrelated to the degree of illness, and may occur in the absence of clinical disease.^{2, 7} Unlike cold hemagglutinins, fluorescent-stainable antibody rises develop in the third or fourth week of illness, persist 12 to 18 months,³² and can be related to immunity against Eaton's PPLO.^{7, 41}

Complement Fixation with Eaton's PPLO. Recently described is a complement-fixation technique for diagnosis of Eaton PPLO infections, using as antigen organisms propagated in broth culture.⁶ This procedure may be adaptable to diagnostic laboratories equipped to perform other complement-fixation tests when standardized reagents become available. Data presented by Chanock et al.⁶ indicate that this serologic reaction could be found in about 85 per cent of patients having fluorescent-stainable antibody rises to Eaton's PPLO. The procedure is thus somewhat less sensitive than the fluorescent-stainable antibody test; the specificity of the reaction also needs scrutiny, since convalescent-phase sera from patients with atypical pneumonia may fix complement with a variety of heterologous antigens.¹⁴

CLINICAL ASPECTS OF INFECTION WITH EATON'S PPLO

Infections with Eaton's organism produce no pathognomonic clinical features,^{24, 37} and illnesses caused by this agent are indistinguishable from the other infections discussed above unless special diagnostic procedures are used. The disease may occur both sporadically and in epidemics. Available data suggest that the infection is not highly communicable.² The incubation period indicated by results of the volunteer experiments is seven to 14 days for pneumonia, and one to 19 days for nonpneumonic respiratory illness.^{3, 7, 41} The onset of symptoms is abrupt, with fever, headache, malaise, cough and chills frequently present. The most consistent physical finding is rales, which often follow the appearance of pneumonic infiltration seen by x-ray. A hemorrhagic type of myringitis developed in some inoculated volunteers,^{3, 41} but this has not been described in the naturally-occurring infections. Peripheral leukocyte counts are frequently normal, but may vary within wide limits. Symptoms usually abate in three to ten days, although x-ray changes may persist for one to three weeks in untreated cases.³⁰

ILLUSTRATIVE CASE (Fig. 6). A 26 year old Caucasian male was hospitalized following a 2 day history of malaise, headache and chills. Temperature elevations from 102° to 106° F. had been documented 1 day prior to admission, at which time the patient developed a nonproductive cough. The initial physical examination was unremarkable except for the presence of fever. Chest x-ray revealed a pneumonic infiltration in the right upper lobe. Leukocyte counts were normal, and bacterial throat cultures revealed no pathogenic organisms. On the second hospital day the patient's cough became productive, and rales were detected.

EATON PPLO PNEUMONIA

DATA	Day of Illness							
	2	4	6	8	10	12	18	26
Temperature (maximum, °F.)	98	104	106	103	101	99	98.5	98.5
Eaton's PPLO isolated from sputum								
Leukocytes (M/mm ³)	7.4	9.5			10.5			
Polymorph./Lymph. %	60/22	79/13						
Chest X-Ray	A	B			C	D		
Fluorescent Antibody (Eaton)	<10						320	
Complement Fixation	8				64		64	
C-Reactive Protein	+	+			+		0	
Cold Agglutinins	<8	<8			1024		256	
Strep. MG Agglutinins		<20			<20		<20	

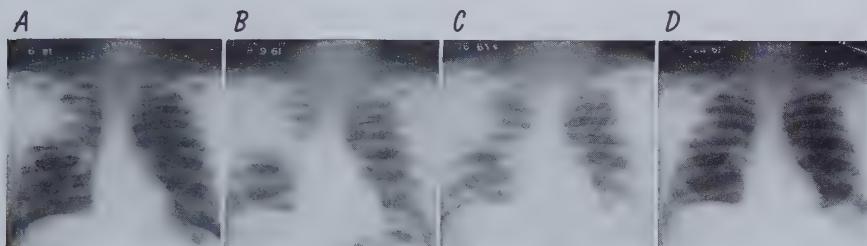


Fig. 6. Illustrative case of Eaton's PPLO pneumonia (see text).

Cultures of the sputum for PPLO revealed a heavy growth of Eaton's organism, and a light growth of *M. salivarium*. Cold hemagglutinin titers rose from <8 to 1024 by the twelfth day of illness. At 3 weeks, titers of fluorescent-stainable and neutralizing antibodies for Eaton's PPLO had increased from <10 to 320; complement-fixing antibody titers changed from 8 to 64 at the same time. There were no demonstrable antibodies to the MG streptococcus.

The patient demonstrated the natural course of Eaton PPLO pneumonia, as shown in Figure 6. Rales were still present on the thirteenth day of illness; physical findings and the pulmonary infiltration had resolved by the twenty-first day.

DIAGNOSIS OF EATON INFECTIONS

Eaton PPLO infections may be diagnosed definitively only by recovery of the organisms, or by demonstration of specific serologic responses. Eaton's PPLO has been isolated from sputa, pharyngeal swabs and throat washings, using cotton rats, embryonated eggs, a

variety of tissue cultures, and artificial media.^{5, 16, 30, 31} The use of artificial media is preferable at the present time because of the adaptability of the techniques to the clinical diagnostic laboratory.

The fluorescent-stainable antibody test has been the most extensively evaluated specific serologic technique for diagnosis of Eaton PPLO infections, but the procedure is technically difficult and available only in the research laboratory. Reagents for the complement-fixation procedure are not yet obtainable commercially, nor has the methodology been adequately evaluated for clinical use.

Cold hemagglutinins should be sought in all patients with atypical pneumonia. It must be emphasized that this nonspecific test is not diagnostic of Eaton PPLO infections, although significant (fourfold) rises in titer are frequently associated with the more severe cases of Eaton PPLO pneumonia. As a prospective diagnostic aid, sera collected early in illness can be tested singly, as well as in comparison with convalescent-phase samples. Initial titers of 32 or greater are usually considered abnormal, and may occur during the first week of illness. The streptococcus MG test adds another nonspecific parameter which can be used, subject to the same deficiencies characteristic of cold hemagglutinins. Agglutinins for the streptococcus MG are found in lower titer and less frequently than are cold hemagglutinins (see Fig. 5).

Technical details concerning diagnostic procedures for Eaton PPLO infections have been compiled by the American Public Health Association.⁹

THERAPEUTIC CONSIDERATIONS

General

Several controlled studies and a number of uncontrolled series evaluating therapy of atypical pneumonia appeared prior to 1956. It is difficult to assess the evidence presented, and much controversy has been generated around the issue of antibiotic therapy in patients with the atypical pneumonia syndrome. In the studies to be considered, diseases were evaluated which did not have an established etiologic diagnosis. Pneumonia due to bacteria, mycobacteria, fungi, and influenza and psittacosis viruses was theoretically excluded from consideration. While many of the patients' illnesses were associated with cold hemagglutinin responses, it cannot be assumed that Eaton PPLO disease was being studied; no means were available for diagnosis of infections due to adenoviruses, parainfluenza viruses, respiratory syncytial virus, and other newly described agents.

Uncontrolled therapeutic trials will not be considered here; results of the controlled series are summarized in Tables 3 and 4. Variations in the experimental protocols of the diverse studies preclude exact comparisons of the data obtained. Several points of dissimilarity are: (1) variations in the severity of illnesses; (2) differences in the duration of illness before therapy was started, and in the total duration of illness; (3) the thoroughness with which known diseases were excluded; (4) considerable variation in the percentages of patients showing cold hemag-

**Table 3. Summary of Controlled Therapeutic Trials in Atypical Pneumonia:
Response Based Upon Defervescence Within 48 Hours After
Initiation of Therapy**

STUDY	ANTIBIOTIC	PER CENT RESPONDING		POSITIVE COLD AGGLUTININS (per cent)
		Treated	Control*	
Meiklejohn, 1949 38 Cases	Chlortetracycline	72	30	93
Hilden, 1950 25 Cases	Chlortetracycline	92	0	—
Schoenbach, 1950 55 Cases	Chlortetracycline	70	23	55
Gallagher, 1952 16 Cases	Chlortetracycline	100	13	100
Homer, 1952 130 Cases	Chlortetracycline	83	89	5
Walker, 1953 212 Cases	Chlortetracycline	36	34	36
Meiklejohn, 1954 147 Cases	Chlortetracycline Oxytetracycline Chloramphenicol	83 83 94	53	—
Kingston, 1961 133 Cases†	Demethylchlortetracycline	45	5	47

* Penicillin, sulfonamides, placebos or no therapy.

† All patients developed fluorescent-stainable antibody to Eaton's PPLO.

**Table 4. Summary of Controlled Therapeutic Trials in Atypical Pneumonia:
Response Based upon the Duration of Fever After Initiation of Therapy**

STUDY	ANTIBIOTIC	AVERAGE DAYS FEBRILE		POSITIVE COLD AGGLUTININS (per cent)
		Treated	Control*	
Harvey, 1949 15 Cases	Chlortetracycline	4	3	8
Peck, 1951 141 Cases	Chlortetracycline	1.6	4.3	12 (treated)
	Chloramphenicol	2.6		39 (controls)
	Streptomycin	1.4		
Wolf, 1956 118 Cases	Chlortetracycline	1.8	0.8	56
	Erythromycin	2.3		
	Oxytetracycline	1.3		
	Tetracycline	1.3		

* Penicillin, sulfonamides, placebos or no therapy.

glutinin responses; and (5) temporal, seasonal and geographic differences in the experiments. Despite these differences, certain generalizations can be drawn from the basic similarities of the studies.

In half of the ten studies under consideration, the investigators concluded that a favorable response was achieved by the test antibiotics^{25, 27, 34, 35, 42} The proportion of patients demonstrating significant cold hemagglutinin responses in these series ranged from 55 to 100 per cent. The average duration of illness in the control groups was less than ten days, and a balanced sampling of degrees of illness was included. In the five studies which indicated no significant response to therapy, cold hemagglutinins developed in from 5 to 56 per cent of patients.^{26, 29, 39, 44, 45} There was considerable difference in the severity and duration of the illnesses described, and the criterion of responsiveness in three of the five studies^{26, 39, 44} was based upon the *average* duration of fever after institution of therapy. No means are available for determining the etiologic agent in the cases of atypical pneumonia comprising these series. The data suggest, on the basis of cold hemagglutinin responses and the natural course of disease, that Eaton PPLO infections may have been predominant in the studies indicating a favorable response to therapy. There is less evidence for associating Eaton's PPLO with the series showing lack of response to the therapeutic agents. It is of interest to compare these studies with the one published report on therapy of atypical pneumonia due specifically to Eaton's PPLO³⁰ (Table 3).

Therapy of Eaton PPLO Infections

The sensitivity of Eaton's PPLO to antibiotics has been studied by several techniques. In general, the data follow patterns established for other PPLO, indicating resistance to penicillin and variable sensitivity to the tetracycline compounds.³⁶ The ultimate answer to the usefulness of antibiotic therapy in Eaton PPLO infections depends upon controlled clinical evaluations in patients with established etiologic diagnoses. At the present time only one such study has appeared (Table 3), which will be discussed below.

SENSITIVITY OF EATON'S PPLO. The effect of various therapeutic agents on Eaton's PPLO has been evaluated by treatment of infected chicken embryos, hamsters, cotton rats and tissue cultures.^{11, 20, 21, 22, 33} Drugs which have been used for this purpose include sodium aurothiomalate, penicillin, streptomycin, chloramphenicol, carbomycin, erythromycin, bacitracin, polymyxin B, oleandomycin, tetracycline and tetracycline derivatives. Experiments using animals indicated that the natural course of Eaton PPLO infection was not affected by penicillin, but was altered significantly by many of these drugs (carbomycin, erythromycin, tetracycline and chlortetracycline). Results obtained by therapy with chloramphenicol and streptomycin have been variable, and depend upon such factors as the strain of Eaton PPLO employed and drug dosages used.

Quantitative sensitivity data are available only from the studies

performed using infected tissue cultures.¹¹ These experiments were designed to include evaluation of the effect of antibiotic concentrations which can be achieved in the sera of patients given recommended doses against standardized amounts of Eaton's PPLO. At the expected range of serum concentrations (0.5 to 1.5 $\mu\text{gm./ml.}$), the drugs which were effective against 10,000 organisms/ml. were tetracycline, demethylchlortetracycline and oleandomycin; at the same levels, streptomycin, chloramphenicol, chlortetracycline and oxytetracycline produced equivocal results. Since the latter group of drugs was used chiefly in the therapeutic trials conducted prior to 1956, another factor is suggested which may have made the responses to therapy difficult to assess. Eaton's PPLO has been found resistant to penicillin, bacitracin and polymyxin B.

CLINICAL THERAPEUTIC TRIAL. In 1961, a controlled double-blind study was performed during an epidemic of Eaton agent pneumonia occurring in Marine recruits at Parris Island, South Carolina.³⁰ The efficacy of demethylchlortetracycline was compared to placebo therapy in 109 patients with Eaton PPLO pneumonia, and in 157 patients with atypical pneumonia due to other causes. Response to therapy was based upon reduced duration of symptoms, signs and x-ray changes.

It was demonstrated that the patients with Eaton PPLO pneumonia who received demethylchlortetracycline responded as compared to the control groups by significant reduction in severity and duration of fever, fatigue, cough, rales and pulmonary infiltrates. The usefulness of demethylchlortetracycline in Eaton PPLO infections was thus documented.

Unfortunately, no other antibiotics have been evaluated for treatment of known Eaton PPLO disease; it should not be assumed, therefore, that demethylchlortetracycline is the drug of choice, nor that other antibiotics may not be clinically effective. Sensitivity data indicate that demethylchlortetracycline and tetracycline are equally effective at the same concentration.¹¹ Oleandomycin is approximately 50 times more potent on the same basis,¹¹ but expected serum levels of this drug are lower following the recommended dosages. The potential toxicity of oleandomycin would seem to preclude its use in Eaton PPLO infections, where the natural course of illness is generally benign, and other effective, less hazardous therapy is available.

Planning Specific Therapy in Atypical Pneumonia

The physician confronted with a patient having the clinical picture of atypical pneumonia has the difficult problem of making a prospective etiologic diagnosis in order to choose appropriate specific therapy. The presence of bacterial atypical pneumonia may be suggested by the leukocyte response, Gram stain examination of sputum, and throat or sputum cultures. Diagnosis of the mycobacterial and fungal infections is more time-consuming, but is aided by epidemiologic information, examination of sputum with the Ziehl-Neelsen and potassium hydroxide techniques, performance of intradermal tests, and appropriate cultures.

While epidemiologic data may suggest the presence of influenza or psittacosis virus infections, distinction of atypical pneumonia due to other viruses and to PPLO presents the greatest diagnostic difficulty. Serologic data are of no prospective value, except for the cold hemagglutinin response which may be developing when the patient is first seen. Techniques for recovery and identification of viruses are difficult and lengthy. Eaton's PPLO is more easily cultivated, but five to ten days are required for the procedures which have been discussed.

Having tentatively excluded bacterial, mycobacterial and fungal disease, the physician's next step is to estimate the clinical severity of atypical pneumonia. Supportive care alone may be indicated in mild cases, for the natural course of that portion of disease amenable to therapy (PPLO) is not significantly altered by the use of antibiotics. In the cases of more marked severity, antibiotic therapy should be instituted. Tetracycline (0.5 gram four times daily) or demethylchlortetracycline (0.3 gram three times daily) may be used, until the patient has been afebrile for 48 to 72 hours. Administration of these drugs for five to seven days would represent an average course of therapy. The photosensitizing effect of demethylchlortetracycline should be remembered in planning treatment for the patient who may be exposed to sunlight.

SUMMARY

Atypical pneumonia is a clinical syndrome which may be caused by bacteria, mycobacteria, fungi, protozoa, rickettsia, mycoplasma and viruses. Those cases associated with rises of cold hemagglutinins and formerly called "primary atypical pneumonia" are due largely to infection with Eaton's agent, which is a pleuropneumonia-like organism (PPLO). Eaton's organism resembles other PPLO in forming microscopic colonies on agar media, showing absolute resistance to penicillin, and in being variably sensitive to the tetracyclines. It differs from PPLO isolated from the human oropharynx in growth characteristics and in possessing ability to lyse mammalian erythrocytes. In addition to cold hemagglutinins and other nonspecific antibody responses, infection with Eaton's organism induces specific neutralizing and fluorescent-stainable antibodies. The clinical picture of Eaton PPLO infections is not distinctive: isolation of the organisms or demonstration of specific antibody rises are needed for diagnosis.

Critical review of controlled studies evaluating therapy in atypical pneumonia suggests that those series favoring use of antibiotics may have included cases of Eaton PPLO pneumonia. Experimental studies indicate that Eaton's organism is most sensitive to oleandomycin, tetracycline and demethylchlortetracycline. Since viral and PPLO pneumonias cannot be distinguished clinically and laboratory diagnosis is usually made in retrospect, therapy with tetracycline or demethylchlortetracycline may be indicated for cases in which other etiologic agents can be excluded.

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Poliomyelitis Immunization—1963

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THE story of the development of effective methods for immunizing against poliomyelitis is not one of triumphant conquest as some feature writers would like to make us believe, nor is it finished. Success in the reduction of cases of paralytic poliomyelitis did indeed come dramatically in 1955 and heartening gains have come since, but the elimination of infection by polioviruses, particularly in the developing countries, may still be a long way off. In any event this report on the status of immunization against poliomyelitis, which bears the date of April, 1963, deals with a subject in transition. Methods are certainly liable to change both as to techniques of administration and immunizing agents employed.

It may not be common knowledge that almost immediately after the discovery of the virus of poliomyelitis in 1909,²¹ efforts to produce a vaccine began. Both killed and live poliovirus vaccines were tried experimentally in monkeys as early as 1910.¹⁵ However, results were meager and it soon became apparent that the task was not simple. Not the least of the difficulties at that time was a lack of appreciation that the poliovirus family was composed of three immunologically separate types. There was also a failure to recognize the extremely widespread extent of human infection with polioviruses of which paralytic cases represent only a tiny fraction. Experimental attempts to develop an antipolio-myelitis vaccine were carried on spasmodically during the period 1910–1930, although it was not until the mid-1930's that efforts to immunize man were made in the United States. These early bold trials were unsuccessful. The "vaccines" at that time were composed of ricinoleated or formalinized antigens, derived from virus-infected spinal cords of monkeys and they embodied certain features which today would be regarded as highly undesirable.

INACTIVATED (SALK-TYPE) POLIOVIRUS VACCINE

After the unsuccessful ventures just related, there was a lag period of more than a decade before the quest for a vaccine was again renewed. By that time—it was after World War II—when Salk began his work under the auspices of the National Foundation for Infantile Paralysis on a formalinized poliovirus

**Table 1. Incidence of Paralytic Poliomyelitis in the U.S.A.
(1951—1962 incl.)***

YEAR	NO. PARALYTIC CASES	YEAR	NO. PARALYTIC CASES
1951	10,037	1957	2,499
1952	21,269	1958	3,697
1953	15,648	1959	6,289
1954	18,308	1960	2,525
1955	13,850	1961	988
1956	7,911	1962	(893)†

* Sources: Surveillance of Poliomyelitis in the United States. Public Health Reports,³² also Morbidity and Mortality Weekly Report, Vol. 10, No. 53, Oct., 1962.

† Tentative figure for 1962 from Report No. 276, March 29, 1963.³³

vaccine of tissue culture origin, the outlook for success was far more promising. One feature particularly in his favor was that he had had recent and extensive experience in testing formalinized influenza vaccine in field trials. By 1954 the Salk-type poliovirus vaccine was ready for its large-scale trial, known as the "Francis Field Trial"¹²—perhaps the severest test of efficacy in the field that a vaccine has ever been given. The trial was a success, and the control of poliomyelitis began to take shape. A number of features had contributed to this real advance. First and foremost was the key discovery by Enders, Weller and Robbins that poliovirus could be successfully grown in tissue culture,⁶ that its presence could be readily recognized histologically, and that this media could furnish virus in adequate titer to be a source of vaccine production. Next came definite confirmation that there actually were three serotypes of poliovirus, each with immunologic specificity, indicating of course that any vaccine should contain a strain of each type if it was to protect against the disease. Thirdly, an extensive experience with formalinized influenza virus vaccine, gained largely during World War II and in the immediate post-war years, had paved the way for the use of inactivated poliovirus vaccine prepared and tested in a somewhat similar manner.³¹

In the years immediately subsequent to 1955, the use of Salk-type vaccine had an impressive impact on the incidence of paralytic poliomyelitis in the United States of America²⁶ and in other countries.⁷ Particularly was this incidence reduced in areas where vaccine of adequate potency had been properly and widely enough used. The decline in the United States (see Table 1) has exceeded 90 per cent.

The current (1962) schedule of doses for the administration of the inactivated (Salk-type) vaccine, recommended by the Public Health Service³⁵ is as follows:

Immunization should be initiated in infants between 6 weeks and 3 months of age according to the following schedules:

NO. OF DOSES	INTERVALS FROM PREVIOUS DOSE
1st	—
2nd	6 weeks
3rd	6 weeks
4th	6 months or longer

The same schedule may be used for other age groups in the interest of achieving higher levels of immunity before the 1962 poliomyelitis season.

After the recommended 4 doses have been administered, additional doses (boosters) are specifically indicated for special reasons, such as the threat of an epidemic or travel to a hyperendemic area.

A few slight alternatives are listed in the 1960 and 1961 recommendations of the American Public Health Association¹ and of the American Academy of Pediatrics²⁷ respectively.

In view of the impressive reduction in the cases of paralytic poliomyelitis in the United States and elsewhere, brought about by the Salk-type vaccine, one can well ask why there should be a question of a substitution unless indeed the inactivated vaccine is to be replaced by a vastly better immunizing agent.

Among reasons why paralytic poliomyelitis did not show a greater reduction in the United States during the period 1956–59 was probably the use of relatively low potency vaccines during that period; but also it was due to a failure during that period and later, on the part of many people, to take advantage of the inactivated virus vaccine for themselves and for their children, particularly children of pre-school age. In 1962 in the United States over 65 per cent of pre-school children and about 70 per cent of young adults, particularly males, had not received the recommended series of four injections. Especially among the lower socio-economic population groups, vaccination programs have lagged. A general lack of interest on the part of some people, which is almost inevitable, may have been responsible, or an unwillingness to submit to a series of 4 inoculations, spread over a year or more. It is still important to determine which has been the most potent reason. However, there are other reasons why the control of this disease through the use of inactivated vaccine still leaves something to be desired. In the United States a few troublesome epidemics have continued to crop up each year during the period 1959–1962, often in well vaccinated populations. In 1962, Australia also experienced a sharp outbreak in an area where inactivated vaccine had been used extensively. While most of the paralytic cases have occurred in unvaccinated or incompletely vaccinated persons, 20 per cent or more have been in individuals with a history of three or more doses of vaccine.

Several factors have been of importance in influencing the current shift toward use of live attenuated poliovirus vaccine in place of the killed vaccine. These include the greater cost of the latter to the individual and to Departments of Health; the innate preference for medication by mouth instead of injection; and the long course of injections which are necessary to build up antibody to satisfactory levels with Salk-type vaccine in susceptible persons, particularly young children.

It is not surprising that changes in prophylactic measures should occur for, as with most therapeutic programs as well as programs of control, techniques are liable to constant modification. The poliomyelitis field is no exception, and not only such changes may concern ways of manufacturing, purifying and administering the inactivated vaccine but they have been concerned with introducing an entirely new kind of vaccine, a live attenuated poliovirus vaccine (Sabin) which has the

advantage of being administered by mouth. It may be that we will see both vaccines in use in this country for the next few years. This does not have to be regarded in the light of a rivalry—the aim of course is to reduce paralytic poliomyelitis to the lowest minimum by the most practical method or methods possible.

THE LIVE, ATTENUATED POLIOVIRUS VACCINE

So much has been written in the last few years in the nature of reviews^{10, 19, 30} and technical papers about this new method of immunizing man against paralytic poliomyelitis that it is unnecessary and certainly impractical to review in detail here the story of its development and the many field trials it has had, together with its widespread use in the Soviet Union and satellite countries, also in Japan, South Africa, England, the United States and elsewhere. A number of these reports have been assembled in the proceedings of various international conferences^{8, 9} and by the World Health Organization.⁷

The principle on which the attenuated poliovirus vaccines is based is similar to that of vaccination against smallpox—namely, that by inducing an actual though harmless infection with a live, avirulent virus, related to that which causes a serious disease, immunity to the serious disease is also induced. The Salk-type vaccine, consisting as it does of an inactivated virus antigen, acts by stimulating certain immune mechanisms including specific antibody formation. One aspect of the efficacy of the Salk-type vaccine is that its immunogenic response limits the chance of spread of polioviruses within the body and particularly within the central nervous system. However, there is little evidence that the antibody levels usually induced by a primary dose of inactivated vaccine alone prevent implantation or multiplication of poliovirus in the alimentary tract. This differs from the situation and from the high and promptly induced levels of antibody following primary vaccination with attenuated poliovirus vaccine. Furthermore, with the live poliovirus vaccine, not only are there postvaccinal circulating antibodies produced, but in addition there develops a kind of local "resistance" presumably resulting from the actual multiplication of poliovirus in association with lymphoid tissue in the alimentary tract. Conceivably this resistance may therefore be "cellular," or it may represent locally concentrated humoral antibody. In any event, it forms a barrier against reinfection and, when such reinfection does occur, it is limited in extent and of short duration.^{17, 24}

The history of live poliovirus vaccines goes back more than a decade when Dr. Hilary Koprowski, at that time an associate of the Lederle Laboratories, began his pioneer work on attenuated strains of type II virus.²⁰ This work was subsequently pursued at the Lederle Laboratories by Dr. Herald Cox. Since 1951, a number of candidate strains representing the three types of polioviruses have been proposed and subjected to trial by different groups of investigators. A major proponent in these developments besides Dr. Koprowski¹⁹ and Dr. Cox has been Dr. Albert B. Sabin^{29, 30} of the Children's Hospital Research Founda-

tion, University of Cincinnati Medical School. To date the attenuated strains that he has developed and tested have been the ones used most extensively throughout the world, and are now licensed in the United States.³⁵

CRITERIA OF ACCEPTABILITY OF ATTENUATED POLIOVIRUS VACCINE STRAINS. Criteria on which certain attenuated poliovirus strains have been selected for use in a vaccine have been based primarily on their lack of, or greatly diminished, neurovirulence when injected intracerebrally, intraspinally or intramuscularly into monkeys. It is thus assumed on fairly good grounds that neurovirulence for monkeys can serve as a measure of pathogenicity in man. None of the attenuated poliovirus strains is completely lacking in neurovirulence for the monkey; and in this connection it should be pointed out that if a poliovirus strain has been so altered or so attenuated that it has lost its capacity to infect man, it would be useless as an immunizing agent. Several attenuated poliovirus strains modified *in vitro* by adaptation to special environmental conditions have proved to be almost completely noninfective for man and as such have been eliminated as candidates for a vaccine.

Acceptability of a given strain to be incorporated into a vaccine has been related to several factors: (a) ability to meet certain criteria of minimum neurovirulence in the monkey; (b) capacity of the strain to achieve a high level (90 per cent or better) of infection and antibody conversion in man, and (c) ability of the manufacturer of the vaccine to meet certain standards of purity, including that of freedom of the product from extraneous agents, such as the simian virus (SV 40).³³ The Division of Biologics Standards of the National Institutes of Health have accepted the Sabin strains as suitable for use in the United States on the basis of meeting these requirements. Types I and II were licensed for use in the United States in August and October 1961 respectively and type III in March, 1962.³⁵

As to the stability of attenuation, or lack of capacity of the strains to revert in the vaccine or his contacts, all of the candidate poliovirus strains that have been studied with care tend irregularly and on occasion to show some degree of reversion on passage through the human intestinal tract. To date, however, a degree of progressive reversion to full virulence and a capacity to produce cases of the paralytic disease in man comparable to that displayed by some wild poliovirus strains is almost nonexistent, and field experience, which by now is very extensive, suggests that, if this has happened, it has been exceedingly rare.

In vitro methods of assaying virulence in attenuated strains are still under study. None seems to be completely reliable at present. There are a number of strain characters (so-called genetic markers), however, which seem to be associated with avirulence, such as: (a) inability to grow at 40° C; (b) delayed appearance of plaques in agar overlay cultures containing low bicarbonate concentrations; (c) reduced growth in a special so-called (MS) cell line as compared to titers in primary monkey kidney cells; etc. However, because there is a lack of complete correlation, biological assay of minimal neurovirulence in the monkey remains

the one property of attenuated polioviruses regarded as the most decisive.

FIELD OBSERVATIONS. From the large number of field trials conducted in 1959-1961, and the rather extensive nationwide use in 1962 of oral poliovirus vaccines, notably in England, Canada and the United States, a wealth of experience has been gained. This experience covers the use of oral vaccines within whole countries, in small and large urban and village communities, both in well and poorly sanitized areas; and within tropical and temperate climates. Several reports have also described the effectiveness of oral vaccine in controlling epidemics of paralytic poliomyelitis. Studies have also dealt with more specific problems: with the spread of attenuated polioviruses in the family¹¹ and in the community;^{14, 18} the duration of virus excretion in susceptible and resistant vaccinees;²⁴ the degree, speed and levels with which post-vaccinal antibody develops in infancy, childhood and adult life; rates at which viremia develops with certain strains of attenuated polioviruses, and the phenomenon of interference induced by polioviruses and non-polio enteroviruses, etc.

SPREAD OF VIRUS TO NONVACCINATED PERSONS. From the earliest days of use of the oral vaccine, questions were raised about its effect upon the immediate associates of the vaccinees and upon the community. Actually, in terms of the sequence of events, the duration of viral excretion, and the capacity to infect familial contacts, the pattern resembles that which follows natural infection, although attenuated strains have less spreading potential than do wild strains.¹⁴ Among family units there are many variables which influence spread; these include the virus strain, socio-economic factors in the family, age of vaccines, number of susceptible siblings, and the presence or absence of concurrent infections with other enteroviruses. All these may influence the likelihood of transfer of attenuated polioviruses. It may suffice to say that in some trials no virus spread at all was noted from the vaccinees to their household associates; in others, the intrafamilial or intra-institutional rate of spread has been low, ranging from 3 to 10 per cent, and in still others to as high as from 30 to 90 per cent. An important observation in this respect was that of Gard et al.¹³ who found rates of spread much higher in familial contacts of children whose age was less than two years than in children above that age. Thus it is in the "diaper age" that spread of the virus is most prominent—an important epidemiological feature. Among features that remain to be determined is the role of dosage in contact spread.

Closely related to this spread of oral vaccine is the question as to how long attenuated polioviruses persist in communities where mass administration has been carried out. Special efforts were made to investigate this point in an urban survey which was carried on in 1961-1962, subsequent to a mass vaccination program in Middletown, Connecticut.²⁸ Here postvaccinally for more than a year, a sample of about 30 infants has been tested at bimonthly intervals; also the urban sewage has been tested weekly. The postvaccinal survey of infants showed that polioviruses persisted in several vaccinated and some unvaccinated children

for about two months. The sewage survey indicated that after the administration of type I vaccine in January, this agent flooded the sewage and was recovered from all specimens tested for a period of six weeks. Similarly, after types II and III, given as a bivalent vaccine in March, these were the predominant enteroviral agents isolated during the subsequent three to four months, with an occasional type I being found during the latter part of this period. After this time, enteroviruses other than polioviruses predominated in the sewage for the succeeding three to four months and polioviruses were encountered only occasionally.

VIREMIA. The question as to whether attenuated polioviruses invade the blood stream was an important consideration in the early days of the accumulation of knowledge with regard to the oral poliovirus vaccines, although it is less so now. Actually viremia has been demonstrated as an accompaniment of infection with some attenuated poliovirus strains, notably with Sabin type II, but not with others including his types I and III.^{16, 23} The occurrence of postvaccinal viremia does not appear to be of great clinical significance in spite of the usual correlation of blood stream invasion and virulence.

GENERAL CONSIDERATION OF SAFETY. From the very beginning of the use of the oral poliovirus vaccines there has been a justifiable fear that attenuated strains may regain their capacity to invade the nervous system of the vaccinee or his contacts. This amounted to more than a suspicion in 1962, for subsequent to the rather widespread use of trivalent attenuated poliovirus vaccines in Canada, there was a small number of suspect cases thought to have been induced by the vaccine. Consequently, in November, 1962, the Canadian Dominion Council of Health recommended that Sabin trivalent oral vaccine not be used alone but should be preceded by an initial course of Salk vaccine.⁴ In the United States also, a number of suspect cases of polio-like illness were reported to have been associated in time with the administration of oral poliovirus vaccine during the summer of 1962. These were carefully reviewed by the Surgeon General of the Public Health Service; his report, issued in December, 1962, designated the numbers of suspected cases which were considered to be compatible with vaccine association, as 11 following type III (of which eight were over 30 years of age); seven following type I (four were over age 30); and none following type II. These suspect cases had arisen after approximately 31,000,000 doses of type I oral vaccine, 19,000,000 type II and 15,000,000 type III doses had been given in nonepidemic areas during 1962. Hence the potential risk was calculated for types I and III to be of the order of 1 per 1,000,000 or less overall, but higher for those over 30 years of age, whereas for type II there was no indication of risk.

As for cases occurring in unvaccinated household contacts, these were practically nonexistent, only two or three being recognized as suspicious cases in the entire country. Considering the large amount of vaccine administered and the expected frequency of spread of the vaccine virus from vaccinated to unvaccinated persons, particularly within homes, it is concluded that the threat of contact spread has so far posed no significant hazard. Taken all in all, therefore, on the basis of the above record

the vaccine was exonerated by the Surgeon General and considered satisfactory for use in the United States.²⁴

ADVANTAGES OF THE ORAL VACCINE. Over and above the evaluation of safety problems of the vaccine by the U.S. Public Health Service in 1962, the attenuated poliovirus vaccine offers a number of advantages. The ease with which it is given, for example a few drops on a lump of sugar or in a teaspoonful of syrup, simplifies individual or mass administration. The relatively short dosage schedule (from four to eight weeks) is convenient and also amenable to incorporation into routine pediatric immunization practice. Thus a single dose of a monovalent vaccine induces a prompt antibody response to the specific type administered in a previously unimmunized person, although a sequence of two or three doses at four to six week intervals is needed for the full course to produce effective immunity against all three types of poliovirus. As already mentioned, a special property of oral poliovirus vaccines is that, besides stimulating antibodies, the vaccinal infection produces a substantial degree of resistance to reinfection in the alimentary tract. Thus the attenuated vaccine offers a tool for rendering children within a community not only individually immune to clinical poliomyelitis, but, if 80 per cent of the children of the most susceptible age have been vaccinated within a given community, a situation is created under which wild poliovirus is largely incapable of spreading. As a result the community as well as the individual has been protected. Furthermore, the oral vaccine is of special use as an anti-epidemic measure if administered early in an outbreak.

One possible difficulty with the oral poliovirus vaccine is the current problem of preservation of the commercial product. At the present time oral poliovirus vaccines must be stored in the frozen state. After thawing, the recommended shelf life is only one week. This disadvantage is slight in community-wide programs, but may be more significant for general office practice. Also, there is a drawback in the possible seasonal variation in its effectiveness, in that nonpolio-enteroviruses may interfere with a "take." Since these enteroviruses are apt to be more prevalent in the summer months, oral vaccines are best administered during the late fall, winter and early spring, except in the face of a threatened epidemic.

AGE LIMITATIONS. The oral poliovirus vaccine should not be given to very young infants, i.e., from birth to six weeks of age, the reason being that a varying proportion of such infants are refractory to infection by attenuated polioviruses, a condition which usually wears off at six weeks of age.^{2, 22}

A question as yet unresolved is whether it is wise to administer the vaccine to adults over 30 years of age since this is the age group in which the few possible vaccine-associated cases have occurred. Actually, the natural immunity rate is extremely high in adults, and if the child population is well vaccinated there would seem to be little opportunity for exposure of the rare susceptible adult. An exception would be parents of young children and those traveling to and within hyperendemic areas.

REACTIONS AND CONTRAINDICATIONS. Reactions are extremely few

and far between, nor are there contraindications other than obvious acute illness. Penicillin sensitivity, recent tonsillectomy or tooth extraction, therapy with steroids, agammaglobulinemia, DPT inoculation and smallpox vaccination are not considered to be contraindications.

The oral vaccine has been given without untoward incidents to premature and newborn babies and the phenomenon of immune tolerance has not been observed.⁹ It has also been given under close observation to several hundred pregnant women and thousands of others have been exposed to vaccinated children. No evidence of ill effects in the mothers, or harmful effects on the fetus have been reported.^{9, 25}

In cases of obvious acute illness, however, it is believed that vaccination should be delayed except for those with minor respiratory infections. The purpose of this is to minimize the possibility of erroneously attributing naturally occurring poliomyelitis to oral vaccine.

CURRENT DOSAGE SCHEDULES. These are subject to change. Since type I cases of paralytic poliomyelitis are usually by far the most common, in some years amounting to 80 per cent of all clinical cases in the United States, it is important, if monovalent vaccines are used, to insure that type I immunity is established first. A current recommendation for use of oral poliovirus vaccine is that it be administered in monovalent form in 3 sequential doses, given 4 to 6 weeks apart. Another alternate schedule which has been used in some states, is that of giving only two doses, namely monovalent type I, followed by a bivalent vaccine, consisting of a combination of types II and III.⁵ The question as to whether a "clean-up" dose of trivalent vaccine, to follow after 6 months or a year, has been seriously considered. A third schedule, which has hardly been used at all in the United States, is to recommend for the initial doses, 2 doses, each of trivalent vaccine 6 weeks apart. This might be followed a year later by a third dose of trivalent.

To recapitulate, a schedule recommended by the Surgeon General of the Public Health Service in March, 1962,³⁵ listed the following:

Oral Vaccine (Monovalent)

- (a) *Infants:* Immunization should be initiated between 6 weeks and 3 months of age and subsequent doses given according to the following schedule:

NUMBER OF DOSES	TYPE	INTERVALS FROM PREVIOUS DOSE
First	I	—
Second	III	6 weeks
Third	II	6 weeks
Fourth	I, II, and III	6 months or longer

- (b) *All Others* (including community use)

NUMBER OF DOSES	TYPE	INTERVALS FROM PREVIOUS DOSE
First	I	—
Second	III	6 weeks
Third	II	6 weeks

The interval may be as short as 4 weeks if vaccination is begun in the spring, or longer than 6 weeks if circumstances require.

There have been certain local modifications of these recommendations. In

some areas the practice has been to combine the second and third dose in a bivalent vaccine. Experience in the duration of immunity produced by this oral vaccine alone is at present limited to 4 years, although with other attenuated strains antibodies have been observed to persist for at least 7 to 10 years.

Pcriodic serum antibody surveys on randomly selected juvenile population groups should provide information on patterns of immunity within the community. On this basis, as well as on the basis of continued surveillance of poliomyelitis, subsequent needs, if any, for so-called "clean-up" doses can be determined.

THE ORGANIZATION OF COMMUNITY-WIDE VACCINATION PROGRAMS

Reasons why mass vaccination is important are inherent with its capacity to break the chain of virus dissemination. There are various descriptions as to programs of this kind carried out in the United States. The objective of any such programs has generally been to vaccinate a maximum number and not less than 80 per cent of the pre-school population in all socio-economic groups.

Optimally, mass immunization campaigns with oral poliovirus vaccines should be conducted during the winter and spring months. The summer months are less advantageous because (1) the higher incidence of other enteric viruses may reduce the effectiveness of the oral vaccines, (2) schools are closed and many people are on vacation, and (3) sporadic cases of poliomyelitis or polio-like diseases may occur coincidentally during the period of vaccination and arouse public concern.

When and if a community-wide program is contemplated, local health departments, working in conjunction with practitioners of medicine, should assume major responsibility in regard to the planning and execution of the program. There should be complete understanding with local health authorities at the start as to the geographic area to be involved in each community-wide program, and as accurate an estimate as possible of the size of the juvenile population, particularly the pre-school age group. Joint planning with all appropriate groups is essential and should include, besides health authorities, appropriate lay groups through which one may reach parents of pre-school as well as school children.

The following points are essential in the development of the community program:

1. The selection of age groups to be vaccinated;
2. Choice of techniques and arrangements for giving the vaccine;
3. The maintenance of records to be available both to the local health department and to private physicians alike;
4. The development of a plan for the maintenance program.

ON-GOING IMMUNIZATION OR MAINTENANCE PROGRAM. This is of the utmost importance and should inevitably follow any community-wide program. It calls for immunization of all infants during the first year of life, those who have escaped previous vaccination, and newcomers entering the community.

Such a program should be conducted in the offices of private practitioners of medicine, by health departments in well-baby clinics, and other community health facilities. It should be carried on throughout the year regardless of season.

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The Treatment of Staphylococcal Infections

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WHILE antimicrobial agents have greatly reduced the morbidity and mortality from most acute bacterial infections, serious staphylococcal disease has continued to pose a difficult therapeutic problem. This problem appears to have emerged in part because of the kind of individuals who acquire staphylococcal infections, and in part because of certain biologic and ecologic factors which set staphylococci apart from other micro-organisms causing acute bacterial disease. These features of staphylococci and the infections they produce must be kept in view when considering general and specific aspects of therapy.

Potentially pathogenic staphylococci are ubiquitous micro-organisms found in normal human beings. They are extremely hardy, and have demonstrated a capacity to acquire resistance to antimicrobial agents.⁴⁸ While nuisance infections caused by staphylococci are common in healthy people, the majority of life-threatening staphylococcal infections occur in individuals with altered host resistance. The very young and the very old, and patients with viral influenza, exfoliative skin diseases, burns, neoplasms, diabetes, hepatic disease, renal failure and those receiving broad-spectrum antimicrobials and/or corticosteroids appear particularly susceptible.^{13, 21, 38, 47, 48} In many instances, the basic host disease is an important determinant of the outcome of staphylococcal infection.

The nature of the staphylococcal lesion per se adds to the therapeutic problem. Staphylococci produce rapid necrosis of tissue with focal abscess formation. While antimicrobials appear to penetrate into abscess cavities,⁴² the large populations of bacteria residing in such closed spaces are often not killed by antibiotics regardless of their *in vitro* sensitivity.^{41, 42, 59} The inability of antimicrobials to eliminate the

enormous populations of micro-organisms present in such collections of pus is a frequent cause of therapeutic failure.

Staphylococci tend to persist within human and animal tissues for prolonged periods of time.⁴⁹ Indeed, in some ways, staphylococcal infections more closely resemble infections produced by tubercle bacilli than infections produced by other gram-positive cocci. Relapse of staphylococcal disease in patients apparently "cured" of their infection is common.

The role of humoral immunity in resistance to or recovery from staphylococcal infections is uncertain. Overt, progressive staphylococcal infection apparently can develop despite the presence of humoral antibodies.^{50, 51} Protective immunity does not appear to follow staphylococcal disease as it does, for example, Group A streptococcal infection.

BIOLOGIC CHARACTERISTICS OF STAPHYLOCOCCI

Although the biologic characteristics of staphylococci of prime importance in determining virulence or the nature of staphylococcal disease have not been clearly defined, certain bear mention as playing a possible role.

Recent observations have suggested that certain strains of staphylococci are relatively resistant to phagocytosis both in the animal body and *in vitro*.^{26, 27, 51} This property apparently resides in surface or capsular antigens, similar to those possessed by virulent pneumococci and streptococci, which retard phagocytosis and account for the animal virulence of these strains.^{26, 27, 39, 62} While most staphylococci associated with human infections do not appear to possess these phagocytosis-resisting antigens when grown *in vitro*, tentative evidence suggests the possibility that other staphylococci may acquire them during growth in tissues.^{27, 52}

Coagulase-positive staphylococci have been shown to survive within human and animal phagocytes.^{37, 46, 60} Such intraleukocytic residence may help spread staphylococci to distant foci within the body, and may protect these micro-organisms from antimicrobial drugs and other antibacterial substances in the surrounding tissues and serum.^{49, 61}

Pathogenic staphylococci elaborate a variety of extracellular products. Of these, coagulase and alpha hemolysin have received most attention. Coagulase production appears to be an almost universal characteristic of staphylococcal strains isolated from instances of primary staphylococcal disease. Under certain experimental circumstances, coagulase may protect staphylococci from phagocytosis or from inhibitory serum factors.^{9-11, 18} However, pathogenic staphylococci are phagocytosed in *in vitro* systems containing coagulable plasma,⁴⁶ and coagulase-negative mutants of coagulase-positive strains can produce disease indistinguishable from that induced by the parent strain.^{20, 33} Thus its role in the pathogenesis of staphylococcal disease remains obscure.

Alpha hemolysin, a rabbit red cell lysin, is elaborated by most strains of staphylococci isolated from human sources.¹² Current evidence suggests that this hemolysin is identical with the extracellular toxin causing skin necrosis and death in experimental animals.^{31, 32, 36} Whether alpha hemolysin plays a role in the pathogenesis of human staphylococcal infection is a debatable question.¹² In certain patients with fulminant staphylococcal disease the clinical picture closely resembles that observed in animals injected with staphylococcal alpha hemolysin. Though it is unlikely that alpha hemolysin plays a part in the initiation of progressive staphylococcal infection,²⁸ it may be an important

determinant of "toxicity" in certain instances of established staphylococcal disease.

Many staphylococcal strains produce the enzyme penicillinase which destroys the antibacterial activity of penicillin G and accounts for the penicillin resistance of these micro-organisms. Other extracellular products elaborated by coagulase-positive staphylococci include a nonhemolytic leukocidin, an enzyme which kills or damages human leukocytes,¹⁵ hyaluronidase, fibrinolysin, lipase, gelatinase, desoxyribonuclease and a human red cell lysis termed delta hemolysin.^{12, 40} The role of these materials in the initiation or maintenance of human staphylococcal disease has not been defined.

GENERAL PRINCIPLES OF TREATMENT

With these considerations in mind, a set of general therapeutic principles for the treatment of serious staphylococcal infections can be proposed.

1. Antimicrobial therapy should be initiated promptly because staphylococci produce rapid necrosis of tissue and quickly grow to high concentrations in abscesses. Early initiation of treatment, while tissue titers of staphylococci are low, may result in eradication of the micro-organisms. However, if treatment is delayed until the number of staphylococci has approached that observed in abscess cavities, little microbial killing occurs and chronic infection can become established.^{34, 41, 49} Thus a delay of 24 hours in recognizing a staphylococcal pneumonia or bacteremia may make the difference between complete recovery or extensive tissue damage and/or death. When serious staphylococcal disease is suspected, cultures should be obtained and appropriate antimicrobial therapy immediately instituted.

2. Surgical drainage should be carried out whenever feasible because of the inability of antimicrobials to kill staphylococci residing within abscess or empyema cavities. Such drainage, in many instances, may be the most important therapeutic measure instituted.

3. Initial therapy should include antimicrobials effective against both penicillin G-sensitive and penicillin G-resistant strains until the result of *in vitro* sensitivity tests are known. Until recently it was observed that staphylococci isolated outside the hospital setting were often sensitive to penicillin G, while those isolated within hospitals were almost universally resistant to this drug. As more strains of staphylococci isolated from the community at large are becoming resistant to penicillin G, this distinction no longer serves as a useful guide in choosing antimicrobials with which to initiate treatment.

Sensitivity to penicillin G should be determined in every instance of staphylococcal infection. Strains having minimal inhibiting sensitivities of more than 0.39 mcg./ml. by the tube dilution method, or showing no significant zone of inhibition with a 2 microgram penicillin G disc, should be considered to be penicillinase producers.

The bactericidal antibiotics such as penicillin G, methicillin, oxacillin and vancomycin, appear to be superior to the bacteriostatic drugs such as erythromycin, chloramphenicol, novobiocin and the tetracyclines, in treating deep-seated staphylococcal infections.

4. The slow response of deep-seated staphylococcal infections, even to the most effective antimicrobial program, should be borne in mind when evaluating therapy. Often 48 to 72 hours pass before fever shows a downward trend, and ten days to three weeks may elapse before temperature returns to normal (see Fig. 3). A rapid downhill course over the first 48 hours of treatment, or no change in the fever curve for four days or more calls for a re-evaluation of therapy. The adequacy of antimicrobial treatment may be roughly checked by determining the serum bacteriostatic or bactericidal activity. The patient's serum should inhibit the growth of the offending staphylococcus at a 1:4 dilution, and when dealing with endocarditis should kill at this dilution. Failure to do so requires an increase in the dose of the drug employed, or a change to another bactericidal antimicrobial effective *in vitro* against the infecting staphylococcus. Persistent fever and leukocytosis in the face of adequate serum antimicrobial activity suggests the presence of an undrained, pus-filled lesion (empyema, splenic abscess, myocardial abscess, lung abscess, etc.), or superinfection.

5. Therapy of serious staphylococcal disease must be prolonged. Staphylococcal pneumonia or bacteremia should be treated for a minimum of four to six weeks. If endocarditis is suspected a minimum of six to eight weeks of treatment is advisable. Evidence of persistent infection should prolong treatment several weeks or occasionally two to three months.

THERAPEUTIC AGENTS USED IN TREATMENT OF STAPHYLOCOCCAL INFECTIONS

The Penicillins

The penicillins are the agents of choice for treating staphylococcal infections. Penicillin G is the most potent antistaphylococcal drug available and should always be employed to treat infections produced by sensitive strains. However, the ability of many staphylococci to produce the enzyme penicillinase has greatly diminished its clinical value. The synthesis of 6-aminopenicillanic acid reported in 1959³ was soon followed by the development of several penicillinase-resistant penicillin homologues which retain their antistaphylococcal activity in the presence of penicillinase.^{25, 56, 57} These agents are definitely the present drugs of choice for infections caused by penicillin G-resistant staphylococci. Two such preparations currently available in this country are methicillin and oxacillin.

The penicillins are bactericidal, well tolerated, nontoxic drugs. As noted in Figure 1, penicillin G is considerably more active against coagulase-positive strains of staphylococci which do not produce penicillinase than either oxacillin or methicillin. However, as seen in Figure 2, oxacillin and methicillin are considerably more active than penicillin G against strains of staphylococci that produce penicillinase. On a weight basis, oxacillin is several times more active than methicillin against coagulase-positive staphylococci but this penicillin is significantly bound to serum protein while methicillin is not. In the presence of 50 per cent

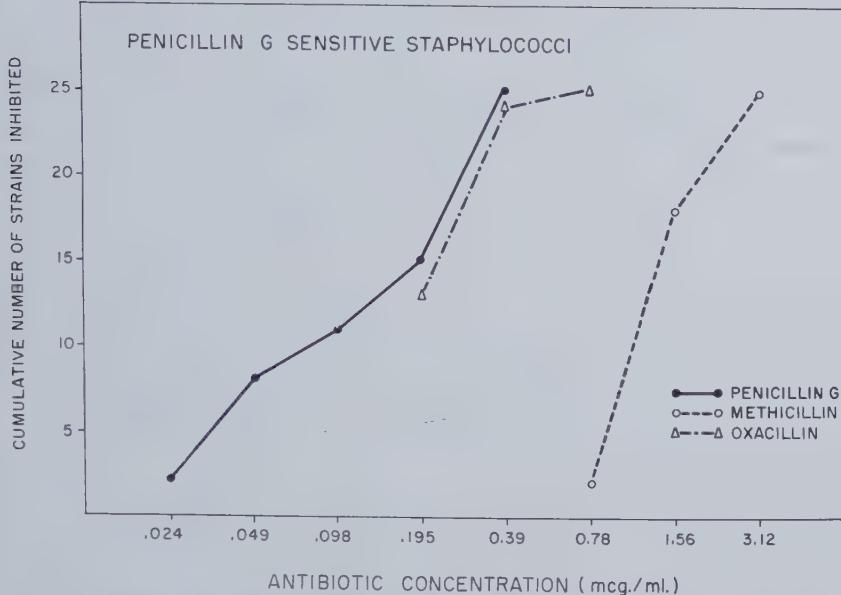


Fig. 1. Minimal inhibitory antibiotic sensitivities of 25 consecutive penicillin G-sensitive staphylococcal strains recently isolated at Vanderbilt University Hospital.

pooled human serum, a two- to eight-fold increase in oxacillin is needed to achieve minimal inhibitory endpoints.^{30, 57} Methicillin is not similarly affected by the presence of serum. The significance of the *in vitro* serum binding of oxacillin is not clear, but despite this apparent drawback good therapeutic results have been achieved with this drug.^{14, 30, 53, 58}

UNTOWARD REACTIONS. The manifestation of allergic hypersensitivity constitutes the most serious untoward reaction to the penicillins. Some patients with histories suggestive of allergy to penicillin G have taken methicillin and oxacillin without difficulty. Because the allergenic properties of the penicillins seem to reside in a portion of the basic 6-amino-penicillanic acid molecule,⁵⁶ it is likely that allergic cross-sensitivity exists between all the penicillins and neither methicillin nor oxacillin should be administered to patients with histories of allergy to penicillin G without extreme caution.

Several other untoward reactions have been noted to occur during methicillin or oxacillin therapy which have not been observed with penicillin G. These have included possible instances of nephrotoxicity,¹⁹ and granulocytopenia^{43, 58} observed during methicillin therapy; and transient elevations of the serum glutamic oxaloacetic transaminase (SGOT) which have occurred during treatment with oxacillin.⁵⁶ We have observed a reversible peripheral eosinophilia as a frequent finding during treatment with both drugs. It is possible that other toxic reactions to these newer penicillin homologues will be observed after they have been used more widely.

Whether or not staphylococci will develop resistance to these drugs is a question that only the passage of time can settle. Coagulase-negative staphylococci develop resistance to methicillin *in vitro* and *in vivo*,⁵⁶ but to date the vast majority of coagulase-positive strains have retained their sensitivity to this

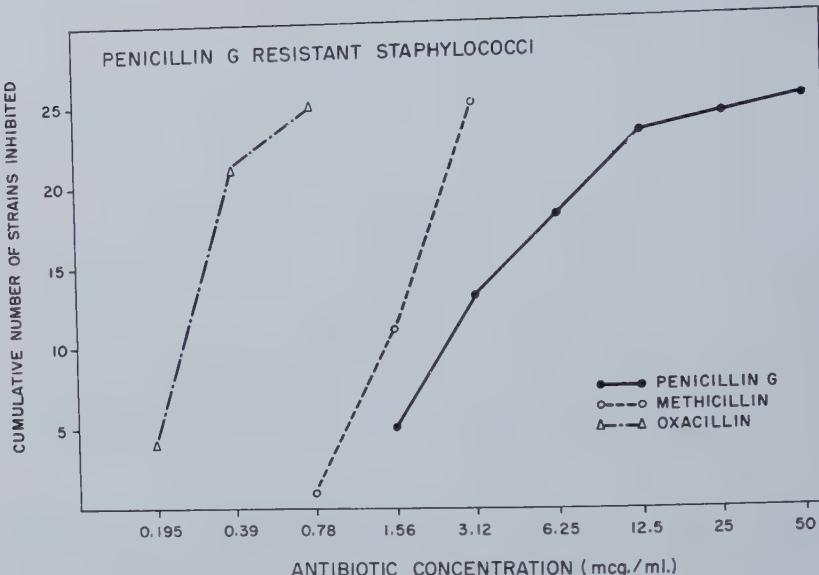


Fig. 2. Minimal inhibitory antibiotic sensitivities of 25 consecutive penicillin G-resistant staphylococcal strains recently isolated at Vanderbilt University Hospital.

drug. Very few resistant strains have been isolated from patients, and these have apparently not been instances of progressive infection.⁷ While methicillin-resistant coagulase-positive staphylococci have been developed *in vitro*, these micro-organisms may be reduced in virulence.⁵⁶

Because of the possible induction of resistant strains, *the penicillinase-resistant penicillins should be used only in the treatment of infections from which penicillin G-resistant staphylococci have been isolated.* There are no other situations in which their use can be justified at this time.

DOSAGE AND ADMINISTRATION OF THE PENICILLINS IN SERIOUS STAPHYLOCOCCAL DISEASE. On the basis of our experience and that of others,^{1, 4, 14, 53, 54, 57, 58} the following recommendations can be made for the use of the penicillins in treating serious staphylococcal disease. These are summarized in Table 1.

1. *Initiation of Therapy.* Before the *in vitro* sensitivity of the infecting staphylococcus is known, treatment should include large doses of aqueous penicillin G *plus* methicillin. This combination of drugs is not antagonistic,⁵⁵ and affords optimal treatment for both penicillin G-sensitive and resistant strains. Aqueous penicillin is most conveniently administered by continuous intravenous drip delivered through a 21 gauge, thin-walled scalp vein needle, in doses of at least 20 million units per 24 hours for adults, and 3 to 10 million units for infants and children.

Methicillin must be given parenterally at four hours intervals. The intramuscular route is usually employed. Initial doses of 2 grams every four hours for adults and 100 mg. per kg. of body weight in divided doses every four hours for children are recommended. If the existence of bacteremia or endocarditis is ruled out, the dose can be cut in half. If

Table 1. The Use of the Penicillins in Staphylococcal Disease*Initiation of Therapy (Before Results of Sensitivity Tests are Known)*

Penicillin G 20,000,000 units per day by continuous intravenous drip (3 to 10 million units for infants and children)

plus

Methicillin 2 gm. every 4 hours intramuscularly or intravenously (100 mg. per kg. daily in divided doses for children)

Continuation of Therapy

A. Penicillin G-sensitive staphylococci

 Penicillin G alone

B. Penicillin G-resistant staphylococci

(1) If bacteremia proved:

 Continue initial dose of methicillin alone for 10 to 14 days, then reduce dose to 1 gm. every 4 hours (50 mg. per kg. of body weight in divided doses for children)

or

 Switch to oral oxacillin

(2) If bacteremia not proved:

 Methicillin alone, 1 gm. every 4 hours (50 mg. per kg. daily in divided doses for children)

or

 Switch to oral oxacillin

Use of Oral Oxacillin

A. After successful initial therapy with methicillin—

B. For initial treatment of wound infections, skin infections, etc.—

 Oxacillin 1 gm. every 4 hours p.o. (100 mg. per kg. daily in divided doses for children)

methicillin cannot be administered intramuscularly (e.g., the patient is in shock, or a bleeding disorder precludes the use of the intramuscular route), it can be administered intravenously. The preferable method of intravenous administration is to dissolve the drug in 50 to 100 cc. of 5 per cent dextrose in water and administer it via syringe over a five to ten minute period directly into a vein or into the tubing of a continuous intravenous infusion set. As methicillin is quite unstable at acid pH and normal saline and 5 per cent dextrose in water are acid solutions, methicillin should never be administered by continuous intravenous drip unless the infusion fluids are buffered. Eighteen to 25 mEq. of sterile sodium bicarbonate solution usually are sufficient to adjust the pH of 1000 cc. of 5 per cent dextrose in water to 7.2 to 7.4.^{56, 57} Even if such precautions are taken, the infusion should be changed every eight hours.

If *in vitro* sensitivity tests prove the infecting staphylococcus to be sensitive to penicillin G, the methicillin should be discontinued and penicillin G alone utilized throughout the therapeutic course. If the responsible staphylococcus is resistant to penicillin G, methicillin (or oxacillin) alone should be continued. If patients with bacteremia or endocarditis fail to respond to initial therapy, the methicillin dose should be progressively increased until 20 to 30 grams a day are administered intravenously. If initial response is good, the dose can be reduced to

STAPHYLOCOCCUS AUREUS BREAST ABSCESS, SEPTICEMIA,
AND PNEUMONIA

(J.M. age 29 WF)

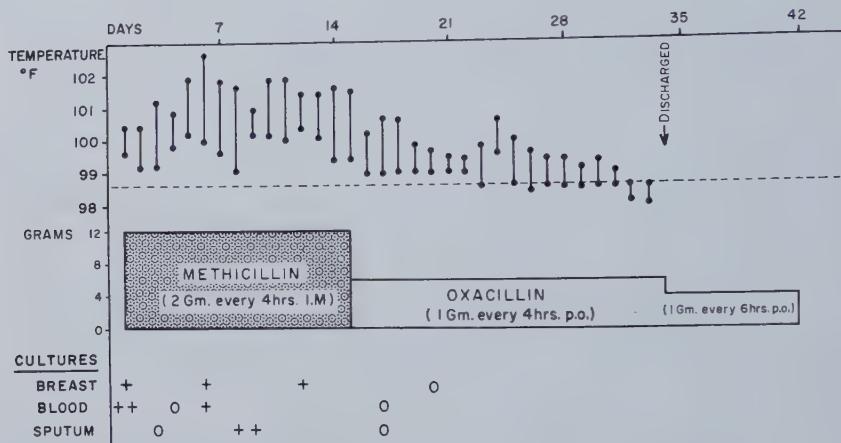


Fig. 3. The course of a patient with a staphylococcal breast abscess, septicemia and metastatic pneumonia treated initially with intramuscular methicillin and then oral oxacillin. Note the slow return of temperature to normal.

1 gram every four hours or the patient switched to oral oxacillin after 10 to 14 days.*

2. *Oral Oxacillin Therapy.* Oxacillin can be administered orally. Some individuals do not absorb this drug well and for best results it must be taken on an empty stomach. Oxacillin is indicated in the treatment of penicillin G-resistant staphylococcal infections under the following circumstances:

(a) Patients with serious staphylococcal disease who have responded well to initial therapy with parenteral methicillin may receive further treatment with oral oxacillin. Such a situation is illustrated in Figure 3.

(b) Patients with less severe staphylococcal disease such as wound infections, cellulitis, pyoderma and other skin infections requiring drug therapy may be treated with oxacillin.

Oral oxacillin should be administered on an empty stomach preferably one to two hours before meals, in doses of 1 gram every four hours. The recommended dose for infants and children is 100 mg./kg./day in four to six divided doses. For children weighing over 40 kg., adult doses should be utilized. Determinations of serum levels or serum activities may be required to assure that adequate absorption is taking place.

Nausea and diarrhea are occasional side effects of oral oxacillin treatment and may be particularly troublesome in children, but in our experience they have not necessitated cessation of therapy in adults.

* It is likely that a parenteral preparation of oxacillin will be available by the time this paper appears. Our preliminary results with this agent indicate it to be as effective as methicillin. Intramuscular doses of 500 mg. every 4 hours have resulted in good serum activities, though for patients with bacteremia or endocarditis 1 gm. every 4 hours should probably be the initial dose.

3. *Administration of Probenecid.* The tubular blocking agent probenecid will successfully increase the levels of penicillin G, methicillin and oxacillin.^{56, 57} Because this drug causes a significant number of allergic reactions it should not be used routinely. In instances of staphylococcal endocarditis in which high antimicrobial serum levels are a necessity, probenecid may be useful in raising methicillin or oxacillin levels, especially where expense or difficulty in administration prevents an increase in the dose of these agents.

Vancomycin

Vancomycin is the drug of choice in treating patients with serious staphylococcal infections who are allergic to penicillin. This is a bactericidal agent that is almost universally active against coagulase-positive staphylococci regardless of their sensitivity to penicillin G. Its clinical efficacy has been well documented.^{8, 22, 35, 63}

Vancomycin must be administered intravenously. The usual daily dose is 2 to 3 grams for adults or 10 mg. per kg. of body weight for infants and children. The appropriate dose is dissolved in 200 ml. of isotonic sodium chloride solution or 5 per cent dextrose in water and is given through a thin-walled, 21 gauge, scalp vein needle over a 30 to 40 minute period at intervals of six to 12 hours. In infants and young children it may be convenient to add the drug to the daily fluid allotment and administer it by continuous intravenous infusion over a 24 hour period.

Side effects produced by vancomycin include fever, phlebitis and eighth nerve damage, especially in those patients with impaired renal function. Febrile reactions may often be reduced by the administration of an antihistamine drug and by decreasing the rate of infusion. Phlebitis can be minimized by employing a scalp vein needle and alternating the site of infusion. The drug should be used with caution in patients with renal disease and azotemia. Full therapeutic doses should not be given under these circumstances, and the adequacy of dosage should be periodically checked by determination of serum levels or serum activities.

Other Antimicrobials

The development of the penicillinase-resistant penicillins and vancomycin has relegated several antimicrobial agents formerly employed in treating staphylococcal infections to a minor or secondary role.

Bacitracin and *kanamycin* are two bactericidal antibiotics with good anti-staphylococcal activity. However, the severe nephrotoxicity of bacitracin and the renal and eighth nerve toxicity and tendency of staphylococci to become resistant to kanamycin have markedly limited their usefulness in staphylococcal infections.

In most communities the majority of staphylococcal isolates are sensitive to the bacteriostatic drugs *erythromycin*, *chloramphenicol* and *novobiocin*. However, it is the writer's opinion that these agents should not be employed in the primary therapy of severe staphylococcal infections. Their use would appear justified only under the following circumstances:

- (a) For prolonged follow-up treatment of patients with serious staphylococcal

disease, whose infections have been controlled with one of the penicillins or vancomycin.

(b) For treatment of relatively minor superficial staphylococcal infections in ambulatory patients who are allergic to penicillin.

In choosing one of the above agents, the following facts should be considered:

1. Fatal aplastic anemia and agranulocytosis have occurred after the use of chloramphenicol and this drug should not be used when sensitivity tests indicate a safer agent can be employed.

2. Novobiocin produces fever and morbilliform rash in up to 10 per cent of patients receiving this drug. A yellow tint to the skin and sclera has also been observed in patients taking novobiocin. While this is usually produced by a metabolite of the drug, a defect in the conjugation of bilirubin has been implicated in some cases.

3. Erythromycin produces few side effects except for minor gastrointestinal upsets. However, approximately 40 per cent of staphylococci resistant to penicillin G are also resistant to erythromycin.

Antisera, Toxoids and Vaccines

Staphylococcal antisera, toxoids and vaccines enjoyed considerable popularity prior to the antimicrobial era but the biologic basis for their use rests on shaky foundations. Evidence for their efficacy has not been convincing, and has often been derived from uncontrolled clinical impressions.¹² Most adults possess a variety of antibodies to staphylococcal exotoxins and cellular antigens, but the role of these antigens in the pathogenesis of, or the humoral antibodies in resistance to human staphylococcal infections is uncertain.

Prior to the introduction of antimicrobial drugs, limited therapeutic success was claimed for staphylococcal antitoxic serum in the treatment of acute systemic staphylococcal infections.^{6, 23, 44} With the advent of antibiotics, such therapy was discontinued by most physicians. Until a carefully designed, well controlled study indicates that superior therapeutic results may be achieved by combined antiserum-antimicrobial treatment, the use of antiserum cannot be recommended.

Staphylococcal alpha toxoids have also been used extensively in the treatment of chronic or recurrent skin infections despite the absence of differences in the anti-alpha toxin titers of the general population and patients with staphylococcal skin lesions.⁴⁵ The results of such therapy have been recently reviewed.¹² Observations are uncontrolled and the numbers of therapeutic failures are impressive. While toxoid treatment still has many advocates, favorable reports must be viewed in the light of spontaneous long-term remissions which are known to occur during the course of cutaneous staphylococcal infections.

The use of various somatic antigens of staphylococci, including autogenous whole cell vaccines, in the prevention and treatment of chronic staphylococcal infections has been generally unsuccessful. Studies reporting favorable results have been uncritical. A recent report on the efficacy of a polyvalent staphylococcal vaccine which also contained bacteriophage revealed it no more effective in reducing the incidence of recurrent furunculosis than a placebo.⁵

Recent work suggesting that antibodies to staphylococcal leukocidin may be of importance in protection from staphylococcal disease,^{16, 40} and a demonstration of antibacterial immunity in an experimental mouse infection²⁶⁻²⁸ has kept alive the hope that an effective staphylococcal vaccine can be developed. On the basis of present evidence, however, no antiserum, toxoid or vaccine preparation can be recommended for the treatment or prevention of staphylococcal disease. It remains possible that new knowledge of the immunobiology of staphylococci may lead to the successful development of such a product.

SPECIAL THERAPEUTIC SITUATIONS**Acute Staphylococcal Osteomyelitis**

Treatment of acute staphylococcal osteomyelitis has certain special problems.²⁹ Therapy should be initiated with large doses of aqueous penicillin G and methicillin. If the infecting staphylococcus is sensitive to penicillin G, methicillin can be discontinued. If the responsible strain is resistant to penicillin G, treatment with methicillin or oxacillin alone should be continued. Vancomycin is the drug of choice in individuals allergic to penicillin.

The affected part should be promptly immobilized in such a manner that repeated examinations and re-evaluation of the progress of the disease can be performed. Obvious collections of pus in soft tissues and subperiosteal abscesses should be drained as soon as the patient's clinical condition permits. Extreme local bone tenderness suggests the presence of intramedullary pus under pressure which may compromise blood supply and produce more devitalized bone. In patients showing persistent or increasing local bone tenderness despite adequate antimicrobial therapy and immobilization, decompression of the marrow cavity is advisable. Wide incision or resection of involved bone is not indicated.

Antimicrobial treatment must be continued for a minimum of three to four weeks, even in patients showing steady improvement. Disappearance of fever and pain, return of appetite, weight gain, remission of leukocytosis and fall in sedimentation rate are generally indications of improvement. Any doubt about the adequacy of response calls for a prolongation of treatment by several weeks.

Superficial Infections

In most instances, superficial infections do not require antibiotics. If *staphylococcal cellulitis* or *lymphadenitis* is present, antimicrobial therapy is indicated and should be continued for 14 days. Surgical drainage is indicated whenever a fluctuant lesion is approachable.

Currently there is no thoroughly satisfactory therapy for *staphylococcal furunculosis*.² Systemic antimicrobial therapy for furunculosis is not recommended except in the presence of rapidly spreading lesions, or where fever or other constitutional reactions are in evidence. Once the local skin abscess has become established, antibiotics are not likely to be effective.

Adequate drainage of the local skin abscess is an immediate objective of therapy. This can be facilitated by the application of hot, moist compresses and surgical drainage when the lesion is fluctuant. An attempt to lessen heavy skin contamination should be made by cleaning the skin around the abscess with a germicidal agent such as Phisohex or 70 per cent alcohol after each application of compresses. The use of zinc oxide ointment or one containing neomycin or bacitracin around the local abscess may prevent skin maceration and the development of satellite lesions. Spread of staphylococci to other areas of skin may be reduced by an absorbent gauze dressing affixed by cellophane tape. Showers with germicidal soaps should be taken three or four times daily to keep skin

staphylococcal counts low, and clothing should be changed after each bath. Bedclothes, including pajamas, must be changed daily and pillows and mattresses should be covered with plastic materials and cleansed daily. All clothing that cannot be washed should be dry-cleaned or exposed to the sun for several hours. Cultures of the patient's nasopharynx and perineum should be obtained when he is first seen and if they reveal coagulase-positive staphylococci, an attempt to interrupt the carrier state may be made by the frequent application (four to five times a day) of topical antibiotic ointments containing neomycin or bacitracin. Because family infection is common in households harboring a patient with active furunculosis, cultures of the skin, nasopharynx and perineum should be obtained on all household members and, if positive, these individuals should also take frequent baths with germicidal soaps and apply topical antimicrobials to carrier sites. Such a program must continue for several weeks after the last overt lesion has cleared, and patients should probably continue to use a germicidal soap indefinitely.

Recurrent furunculosis is an extremely frustrating disease for both patient and physician. Adherence to a regimen as outlined above, liberal doses of reassurance and support, plus passage of time, are the best therapeutic measures we can apply at this time to the treatment of this unpleasant disorder.

Treatment of Asymptomatic Nasal Carriers

The role of the asymptomatic nasal carrier of coagulase-positive staphylococci in the epidemiology of hospital-acquired staphylococcal infections is a subject of debate. At present it would appear advisable to remove hospital personnel who are carriers from critical areas such as operating rooms, delivery rooms, nurseries and surgical floors. In some individuals, temporary removal from the hospital environment will eliminate the carrier state. Unfortunately, other methods of treatment have not proved completely satisfactory.

It has been shown that systemic antibiotics only suppress staphylococci within the noses of adults,²⁴ and the expense and possible toxic and sensitizing effects of the drugs employed make such treatment impractical. Limited success has been achieved in treating carriers with intranasal ointments containing neomycin, bacitracin or a combination of drugs.¹⁷ However, the effect is often suppressive and may last only for a few days. Recently, intranasal methicillin was shown to permanently eliminate coagulase-positive staphylococci from one-third of a group of nasal carriers.⁶⁴ However, because of the possibility of increasing the number of resistant strains, it would not appear wise to use methicillin for such therapy.

At present the most reasonable approach to the treatment of persistent, asymptomatic nasal carriers includes removal from the hospital environment, taking of frequent baths with germicidal soaps, and the use of antibiotic ointments containing bacitracin or neomycin intranasally four to five times daily for two weeks. If the carrier state returns within several weeks, a second course of treatment is indicated.

SUMMARY

Serious staphylococcal disease continues to pose difficult therapeutic problems. Successful management depends on early institution of appropriate antimicrobial therapy; surgical drainage of pus-filled lesions when they are accessible; and prolonged antibiotic treatment with appropriate bactericidal agents.

Presently available antisera, toxoids and vaccines cannot be relied upon for the treatment or prevention of staphylococcal infections.

There is no satisfactory treatment for recurrent staphylococcal furunculosis. The use of germicidal soaps and topical antibiotics to reduce staphylococcal counts on the skin and carrier sites may be helpful. Other staphylococcal carriers who may serve as a source of exogenous reinfection should be treated in the same way.

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Hospital Staphylococcal Infections

Interruption of Transmission as a Means of Control

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HOSPITAL-ACQUIRED staphylococcal disease continues as an ever-present threat to patients whose problems require inpatient care. The tragic case report which follows is typical of the too frequent disasters which occur as untoward complications of hospitalization.

CASE REPORT. During a routine physical examination this 6 year old boy was found to have absent femoral pulses and blood pressures of 150/80 in the arms and 90/80 in the legs. He was scheduled for surgery, but postponement for 3 weeks was necessary because of a respiratory infection for which he was given penicillin. Subsequently, surgical excision of the coarctation and primary anastomosis of the aorta was easily achieved, and he was discharged on the tenth postoperative day. Two days later he returned, acutely ill with a temperature of 40° C. His leukocyte count was 23,000 with 85 per cent neutrophils. Eight consecutive blood cultures yielded a hemolytic *Staphylococcus aureus*, coagulase positive, and resistant to most antibiotics. Fluoroscopic and x-ray studies demonstrated a mass in the superior mediastinum pushing the esophagus to the right, and an aortogram a few days later showed that the mass was an aneurysm at the anastomotic site. He was treated intensively with methicillin, chloramphenicol and erythromycin. Although his fever slowly decreased, the aneurysm ruptured 18 days after readmission (4 weeks postoperatively) and he died.

Examples of such tragedies as this can be found in almost any hospital record room. Fortunately, most hospital-acquired staphylococcal infections are not so disastrous in outcome as in this case; nonetheless the more frequent minor infections are also important because of the inconvenience, discomfort and expense which result.

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In the following discussion, the term "staphylococcus" refers to *Staphylococcus aureus*, coagulase positive.

THE PATIENT POPULATIONS AFFECTED

Three groups of patients appear to account for most of the staphylococcal disease acquired in hospitals. The first of these comprises newborn infants. The occurrence of epidemics of illness both within the nursery and in infants and their families subsequent to discharge is well documented; it is not known whether nursery-derived staphylococcal disease has become more frequent in recent years or whether the combination of increased awareness on the part of the physician plus a decrease in other scourges of early life (such as epidemic diarrhea of the newborn) has made staphylococcal disease more obvious.

Surgical patients comprise the second group of patients endangered by staphylococcal disease. Numerous outbreaks of postoperative infections have been recorded. However, life-endangering disease does not appear to have actually increased in patients undergoing surgical procedures which by present-day standards might be considered relatively minor. Thus, Barnes et al.² showed that the incidence of postoperative wound infections in patients undergoing herniorrhaphies or hysterectomies at the Massachusetts General Hospital did not change between 1937 and 1957. Other data, however, suggest that changes in the types of patients submitted to surgery, the development of radical surgery, and certain aspects of therapy have provided a postoperative population which does exhibit a high risk of sepsis.¹ The willingness of the surgeon to operate upon patients who in the past would have been considered too old or too debilitated may well have increased the rate of severe postoperative infection. In addition, the ability to attack surgically lesions formerly considered inaccessible or inoperable also appears to have resulted in more severe infections, if for no other reason than that a staphylococcal infection in the mediastinum following cardiac surgery is because of its location far more serious than an infection in a herniorrhaphy wound. In addition, modern adjuncts to surgical care such as intravenous needles or cannulae used for protracted periods, catheters, tracheotomy tubes and the like provide ready avenues of entry for organisms.

Finally, some groups of medical patients appear to display increased susceptibility to staphylococcal disease acquired during hospitalization. Certain underlying illnesses, including viral respiratory diseases such as influenza, diabetes, hepatic disease, neoplasms, renal failure and skin disorders,⁶ appear to endanger the patient. In addition, as with surgical patients the medical patient who enjoys the benefits of modern therapeutic achievements also experiences an attendant risk of infection due to compromising of his defenses by these same achievements. Thus, such devices as catheters and cannulae may provide avenues of entry, radiation, antimitotic drugs and steroids may interfere with his protective mechanisms,¹ and antibiotics, while preserving him from the pneumococ-

cus or other organisms more devastating in years past, may predispose him to acquiring a hospital-derived staphylococcus.⁴

POSSIBLE MEANS OF PROTECTING PATIENTS

Clinically significant immunity to staphylococcal infection has not been demonstrated. Though the appearance of antibodies against some antigens elaborated by the organism has been documented,⁸ there is no evidence that these antibodies play any role in protection against staphylococcal disease. In addition, it is not known exactly why patients seriously or chronically ill with other illnesses appear to exhibit increased susceptibility to staphylococcal infection.

Rogers and Louria²⁴ have characterized the present status of the antibiotic treatment of hospital-acquired staphylococcal disease as being unsatisfactory, and have attributed this in part to some of the features of infection with this organism: the rapid development of tissue necrosis and the failure of antibiotics to affect sluggishly metabolizing staphylococci residing in pus, to say nothing of the resistance of hospital staphylococci to most antibiotics. The appearance of a drug (methicillin) to which staphylococci are unlikely to become resistant may well improve somewhat the results of antibiotic therapy of these infections.

Because of the lack of protective host immunity and the difficulties in achieving satisfactory results with treatment of hospital-acquired staphylococcal disease, it is logical to consider the possibility that such infections might be kept to a minimum by preventing the transmission of hospital organisms to patients. However, the physician is handicapped by lack of knowledge regarding the routes by which the organisms are spread; such knowledge is essential to rational control.

STAPHYLOCOCCAL EPIDEMIOLOGY IN HOSPITALS

Most studies of the spread of staphylococcal transmission among adult patients have been conducted in surgical units. Here the critical reader is faced with a mass of conflicting, confusing data from which it is difficult to draw reasonable conclusions concerning either routes of spread or means of effective interruption of such spread. For example, it is not clear whether surgical infections more often arise in the operating suite or on the ward. How often one patient transmits his organism to another is unknown, though it is known that a patient who is a nasal carrier of staphylococci on admission exhibits an increased risk of post-operative wound infection, and that this increased risk is accounted for by infection by his own organism.²⁵ It is clear that surgical personnel who are nasal carriers of staphylococci, especially those in the operating room, are frequently responsible for wound infections.^{6, 22, 25, 27} Whether their organisms are transmitted via the air, by intimate contact or by some other route is unclear.

Most confusing is the role of organisms in the environment. It is well established that the air, floor, fomites and other inanimate objects in

proximity to a patient with staphylococcal disease are frequently contaminated with that patient's organism; however, the recovery of an offending strain from a given site does not necessarily mean that that site is a way-station in transmission. Certainly it has been shown that environmental group A streptococci, though viable on culture, are inconsequential in terms of infectiveness.²³ Comparable studies of the infectivity of environmental staphylococci are not available. Unfortunately, all too often the mere presence of a given staphylococcus at various loci in the environment has been equated with infectiousness, and upon this interpretation are based many present practices directed at controlling hospital infections.

Investigations of routes of transmission of staphylococci in hospitals are seriously handicapped by several factors. First is the ubiquity of the organism, both in terms of numbers of people (personnel, patients and visitors) who are carriers and in terms of the variety of sites in the environment where the organisms may be found. Secondly, the activities and mobility of adult patients in a hospital make it nearly impossible for the investigator to have any confidence in conclusions based on exposure of the patient to other people and sites. Therefore bacteriological surveys of patients, personnel and environment on such hospital divisions present a mass of data which permit a wide variety of conflicting interpretations.

Studies conducted at this institution have been designed in an effort to minimize these two difficulties. Newborn infants constitute a non-mobile patient population, segregated from the rest of the hospital, cared for by limited personnel and without visitors. Furthermore, it has been possible rather simply to modify the environment of newborn infants to provide means by which various sources and routes of spread of staphylococci were limited to those being investigated. It was anticipated in designing these studies that the results might reflect staphylococcal epidemiology among adults as well as infants in hospitals.

In considering the epidemiology of the staphylococcus, it is important first to establish a working classification of the possible routes of spread that exist. Table 1 is a modification of the classical grouping of the epidemiology of respiratory disease. In this classification, *indirect transmission* includes three possible sources of organisms: the air, fomites and the hands of personnel. It is well established that staphylococci are widely dispersed in the air as airborne droplet nuclei containing a single or very few organisms; these droplet nuclei gravitate slowly and may be widely disseminated by air currents. Staphylococci, once settled on the floor or other surfaces, may persist in a viable state for long periods of time in dust. In addition, fomites and other inanimate objects in the environment of patients with staphylococcal disease have been shown to be contaminated by the offending organisms. Furthermore, it is possible that indirect transmission might occur via the hands of personnel in two ways: either a nasal carrier might transmit his organism to patients via his own contaminated fingers (primary physical transfer), or personnel who are not carriers of organisms in the usual sense might transfer organisms between patients via inadequately cleansed hands

Table 1. Possible Routes of Spread of Staphylococci Among Newborn Infants

<i>Indirect Transmission</i>	
Airborne organisms	
Droplet nuclei	
Dust	
Contaminated fomites	
Physical transfer of organisms	
Primary (hands of nasal carrier)	
Secondary (from baby to baby via hands of personnel)	
<i>Direct Transmission</i>	
Intimate contact	
Direct contact	

(secondary physical transfer). *Direct transmission* denotes two routes of spread: heavy drops expelled from the respiratory tract containing thousands or millions of organisms and which settle rapidly within 6 to 8 feet, and direct contact with an open, infected lesion (such as might happen when a physician with a draining paronychia handles an infant).

Nursery Studies

The studies which have been conducted at this hospital and directed at determining the relative importance of these routes of spread have been of two basic designs. In one, the habitat of the newborn infant has been modified in such a fashion that organisms might be transmitted to him from only one or two sources and in only one or two ways; because of the many possible sources and routes of spread normally present in a nursery, valid interpretations might be impossible without such a modified environment. The other type of study has consisted of altering the standard nursery procedure in a manner intended to interrupt or block one route of spread for some infants, retaining others as controls. By comparing the two groups it has been possible in some instances to make reasonable interpretations concerning the importance of the "blocked" route of spread.

Throughout these studies, bacteriophage typing techniques in combination with antibiotic sensitivity patterns have been employed for tracing organisms. Transmission has been considered to have occurred only if an infant became truly parasitized by the organism in question, and not if a few colonies were recovered transiently during or after exposure.

AIRBORNE ORGANISMS. Several of these studies have attempted to define the relative importance of airborne droplet nuclei and dust in the transmission of staphylococci. In the first study³⁰ an attempt was made to compare the relative importance of intimate contact versus airborne organisms. Infants were exposed to a known carrier-infant by being placed in bassinets set at fixed distances from the carrier, or index, baby. Transmission could have occurred only via the air because different personnel cared for the index and study babies. Surprisingly, a very low rate of spread was observed.

Of 91 infants so exposed, only one baby definitely acquired the index baby's strain; seven other infants were parasitized by organisms which possibly were the same as that of the index baby. Thirty of the 91 study babies were sufficiently distant from the index baby that spread could not have been by intimate contact; two possible acquisitions occurred in this group.

Two subsequent studies have indicated that airborne spread of staphylococci between babies does occur, but at a rate too low to account for more than a small fraction of the transmission of staphylococci in a nursery. One of these studies²¹ indicated that physical transfer of organisms between babies by the hands of personnel was more important than airborne organisms and intimate contact combined. The other study²² likewise demonstrated a very low rate of airborne transmission which resulted in parasitism, even though it was shown that viable organisms were freely transported through the air to the exposed infants.

ORGANISMS ON FOMITES. Studies of fomites in contact with infants have indicated that such objects in the environment of carrier-infants are readily contaminated with staphylococci.¹³ Indeed, personnel-carriers who handle blankets, linen, etc. often deposit viable samples of their staphylococci on these surfaces. However, transmission via such fomites appears to be inconsequential,¹³ presumably because the number of contaminating organisms is insufficient to infect.

PHYSICAL TRANSFER OF ORGANISMS. This mechanism seems to be the major means by which newborn infants acquire hospital staphylococci. Personnel-carriers appear to transmit their organisms to infants primarily by physical contact.³⁰ In addition, it has clearly been demonstrated under circumstances which permitted transmission by no other route that the hands of such carriers can be infectious.³⁰

Subsequent studies²³ have shown that the hands of personnel readily transfer organisms from infant to infant, and that the usual handwashing procedures are inadequate to prevent an infant from becoming a carrier of another infant's organism by this route. Indeed, the hands of personnel appear to be far and away the most important means by which staphylococci spread in newborn nurseries.

DIRECT TRANSMISSION. These studies have failed to define the importance of intimate contact or direct contact with an open lesion in the transmission of staphylococci to newborn infants. Certainly there can be little doubt that thoughtlessly permitting an open, purulent infection to come in physical contact with an infant or other patient might result in transmission. Whether staphylococci are effectively transmitted from the respiratory tract of carriers is open to serious question. Hare and Thomas¹⁵ have shown that nasal carriers of staphylococci expel very few or no organisms by breathing, talking, coughing and sneezing. Indeed, significant numbers of organisms were released only by "snorting"—a maneuver which is the approximate equivalent of blowing one's nose without a handkerchief.

Circumstantial evidence, however, suggests that organisms in the air are of minor importance epidemiologically compared to physical transfer, at least insofar as newborn infants are concerned. It is well established that staphylococci acquired by newborn infants usually are recovered from the umbilical stump and skin surfaces prior to their appearance in the upper respiratory tract;^{16, 21} it seems likely that organisms transmitted via the air would appear in the nose first. In addition, it has been shown that protection of the skin surfaces and/or umbilical stump against such organisms effectively interferes with colonization.^{12, 19}

Epidemiology Among Adult Patients

Studies similar to those conducted in the newborn nurseries at this hospital would be difficult, if not impossible, to accomplish on adult patient-care units. Indeed, the most informative data concerning routes of spread of staphylococci to adult patients have been derived from the results of attempts to block such spread. Interpretation of these data in relation to the nursery studies suggests that these latter observations may apply as well to adults, particularly those undergoing surgery.

It appears logical to assume that most surgical wound infections are acquired in the operating room. This would be particularly true in the case of deep infections; certainly it is difficult to imagine that the child whose unfortunate case history is reported herein became infected elsewhere (unless he received contaminated intravenous fluids, an unlikely event). Circumstantial evidence derived from outbreaks of surgical infections which could be traced to a single personnel-carrier has provided additional support to the concept that such infections usually originate in the operating room.^{6, 22, 25, 27} In addition, the instillation of antibiotics into wounds at operation appears to prevent at least some infections.¹⁰ However, it also seems logical that open incisions, burns and other wounds might be contaminated on the ward during changes of dressings or other manipulations.

Perhaps the most important question to answer in regard to wound infections in surgical patients, whether they arise in the operating suite or on the ward, is whether the organisms that infect the patient are transported to him via the inanimate environment (air, dust, fomites, etc.) or by the hands of personnel (primary or secondary physical transfer). The available circumstantial evidence suggests that the latter route is of greater importance, as has been concluded from the nursery studies. Perhaps the strongest bit of this evidence is the number of organisms required to infect. It appears that infection in man results only when staphylococci numbering hundreds or thousands are incorporated into a wound;⁹ it is not likely that fallout of organisms, even from heavily contaminated air, would achieve this concentration in a localized area of a wound. Secondly, a variety of studies has been performed in which the environment has been decontaminated; at best these studies have yielded debatable or conflicting results. For example, Shooter et al.²⁶ altered the ventilation in an operating suite and believed that reduction in wound infection rates was a direct consequence. In contrast, Kinmonth et al.¹⁸ and Gillespie and colleagues¹¹ instituted similar measures and noted no difference in rates of infection, even though numbers of organisms in the air were diminished.

In other studies blankets have been oiled or sterilized on surgical wards. Clarke et al.⁷ oiled blankets, screening and floors; a reduction in air-counts of staphylococci but not in nasal cross-infection or wound sepsis was observed. Likewise, sterilization of bedding did not affect infections¹¹ or nasal colonization.²⁰ In contrast, Blowers, Potter and Wallace⁵ sterilized blankets on a ward devoted to the care of burned patients, and observed a decrease in cross infection. However, because

other preventive measures were also introduced, the investigators were unable to draw any definite conclusions.

Clearly the environment of patients with open staphylococcal disease is heavily contaminated with organisms,¹⁴ but the few observations reported herein would suggest that air, dust and fomites are not of great consequence epidemiologically. Thus, it is possible to deduce that the routes of spread of staphylococci to surgical patients are very similar to the routes of spread to newborn infants, as determined in more direct studies. The most important route may well be the hands of personnel, either self-contaminated or contaminated with organisms of infected patients. Surgical gloves do not appear to offer adequate protection against transmission, because a large percentage can be shown to be pervious to organisms.³

It is difficult to draw conclusions concerning the modes of transmission of staphylococci to nonsurgical hospitalized patients. Undoubtedly such patients acquire staphylococci by routes other than physical transfer; it is well known that hospitalized medical patients frequently become carriers of staphylococci acquired during their stay.⁴ It is logical to assume that pneumonia due to a hospital strain of staphylococci in such patients occurs in someone who first becomes a nasal carrier of that organism. Exactly how such a patient becomes a nasal carrier is unclear; whether this represents airborne spread, intimate contact or some other route is unknown.

Certainly medical patients with tracheotomies, catheters, intravenous cannulae and other devices are similar to surgical patients in that these disruptions of anatomic defenses constitute avenues of access to organisms of all types. It is likely that infection through such orifices often occurs, as with any surgical wound. It is not unreasonable to conclude that the major source of organisms that infect via these devices is the hands of personnel, as with newborn infants.

PREVENTION OF TRANSMISSION OF HOSPITAL STAPHYLOCOCCI TO PATIENTS

In the light of the foregoing data and hypotheses it is possible to make reasonable recommendations concerning the prevention of hospital-acquired staphylococcal disease in medical and surgical patients.

1. First, it would appear quite clear that the handling of any open lesion or orifice that is ordinarily sterile, whether it be in the operating room or on the ward, and whether it be the making of a surgical incision, dressing a wound, insertion of a catheter, cannulating a vein or replacing a tracheotomy tube, should be carried out under sufficiently sterile precautions to ensure insofar as possible that contamination will not occur. Physicians and nurses who minister to patients must constantly bear in mind that their hands may serve as a means of mass transportation of organisms to patients—either from other patients or from themselves if they are carriers.

2. Patients and personnel with open staphylococcal disease should be segregated in some way so that they do not come in contact with suscep-

tible patients. Whether such infected hosts transmit via the air, fomites, hands or some other route is of little consequence; it is clear that they do transmit and they consequently should be regarded as individuals with highly contagious diseases.

3. Since many outbreaks of infections can be shown to be due to a single personnel carrier, a workable system by which hospital infections can be recognized, the organisms characterized and possible sources identified should be made available to every hospital. At present the only practicable and reasonably satisfactory means of tracing staphylococci is bacteriophage typing. Since it appears that repeated washing of walls and floors, sterilization of bedclothes, meticulous cleaning of bedside tables and chairs, etc., may well be of no practical use, the same time, effort and money might well be better spent characterizing the organism, defining the extent of the problem, and determining who is the carrier responsible when an outbreak of staphylococcal disease occurs.

4. Patients whose defenses are compromised by therapy should be protected as much as possible from potential sources of hospital staphylococci. They should not be on open wards and preferably they should not be attended by personnel known to be staphylococcal carriers. In addition, it should go without saying that a patient's defenses should not be compromised needlessly; the administration of unnecessary antibiotics is an example of how the likelihood of a patient's acquiring a staphylococcus might be increased.⁴

Future studies may clarify further the routes by which staphylococci spread within hospitals, and with such data more specific means to prevent spread may be developed. In the meantime, it is urged that physicians and other hospital personnel recognize that certain routes of spread appear to be of paramount importance. These routes seem to be intimate and probably physical contact between patients and personnel.

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The Nature and Treatment of Pneumococcal Pneumonia

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"Take pneumonia. It has been treated by bleeding, and got well. It has been treated by brandy, and got well. It has been left to itself, and got well. And the bleeders, the brandy givers, and the doers of nothing at all, respectively, have had a vast deal to say for themselves and against their rivals. And which of them are to be our guides and masters in the treatment of pneumonia? None of them for a single day, much less for always."

PETER MERE LATHAM, quoted by BEAN

Pneumococcal pneumonia is a very common disease, particularly in the patient population of large metropolitan general hospitals. During an average winter week some ten patients are admitted to the wards of the Cincinnati General Hospital and another ten are seen in the emergency room, given initial treatment and subsequently treated in the outpatient clinics. These patients receive one of many varied treatment schedules, depending on the background of training and experience of the resident physicians on duty. The great majority of the patients are adequately treated, although some are not. That a large variety of regimens may now be successfully used in the treatment of a disease that only a few years ago was essentially untreatable, is one of the truly great advances of our age. It is our purpose to attempt to bring this historic progress to the attention of younger physicians and medical students, as well as to reminisce with others. We should then like to suggest what we believe at present to be a proper treatment for the patient with pneumococcal pneumonia.

THE NATURE OF PNEUMONIA: ITS PATHOLOGY AND PATHOLOGIC PHYSIOLOGY

Pneumococcal pneumonia may be either lobar in extent or simply of a lobular or bronchial distribution. Lobular pneumonia is characterized by an acute intra-alveolar exudate of serum, fibrin and polymorphonuclear leukocytes along with myriads of pneumococci occurring in scattered lung lobules. Occasionally the involved lobules may be confluent and the disease becomes almost lobar in extent.

Typical lobar pneumonia is recognized as evolving through several stages. Experimental studies, such as those by Robertson²⁷ and Wood,^{28, 29, 40} have led to a close understanding of the progress and events of the disease.

The initial invasion of the alveoli by pneumococci results in a response by the host consisting of congestion of the blood vessels and a rapid outpouring of edema fluid. This edema fluid serves as a medium for growth of the bacteria and also as a means of spread of bacteria either via the pores of Kohn or intrabronchially.¹⁷ This sharply demarcated zone of edema fluid and bacteria advances peripherally as the initially infected zone provokes the body's defense reaction which consists of outpouring of erythrocytes and leukocytes into the involved alveoli. This reaction plus the vascular engorgement forms red hepatization. At this stage of early consolidation, leukocytes are already actively phagocytizing the bacteria. As the disease progresses, the older, more central areas become packed with leukocytes and in this area of advanced consolidation or gray hepatization the bacteria have been phagocytized and are difficult to demonstrate. With the stage of resolution more macrophages are found in the alveoli, clearing the area of leukocytes.

The immune response to pneumococcal infection consists of the production of antibody to the type-specific capsular polysaccharide of the infecting pneumococcus. The appearance of this antibody^{23, 28} often occurs at the time of onset of the lysis or the crisis. Antibody apparently is not really necessary for either to occur. The antibody may appear several days before or even sometime after the patient has improved.

Antibody enhances phagocytosis of the pneumococcus²⁹ by the leukocyte by an opsonic action on the capsule of the bacteria themselves.³⁷ It was also shown that, in the presence of opsonin, macrophages were more active in phagocytizing pneumococci than were the leukocytes.³⁰ Robertson²⁷ considered the transformation of the fixed tissue cells into macrophages as the second important immune mechanism.

In studying the action of specific antiserum, Wood³³ postulated that the real action of the antibody was to produce an agglutination and opsonizing action on the pneumococci in the edema zone. He believed that there was not enough antibody present to act throughout the consolidated area and felt that the phagocytosis which occurred was due to a non-antibody mechanism.

Study of the action of chemotherapeutic agents in experimental pneumonia revealed the occurrence of a new and different mechanism. Finland et al.¹³ demonstrated that the bactericidal action of sulfapyridine

and the immune mechanism were separate but of assistance to each other. In patients treated with sulfapyridine the bactericidal action was a delayed one which required growth of the bacteria but when it occurred it was completed within three hours. The protective antibodies were rarely developed before the sixth day and agglutinins were rarely observed before the seventh day of the illness.

Wood³⁸ was of the opinion from his studies that antimicrobial drugs have no effect on phagocytosis but because of their action of bacteriostasis they stop the multiplication of bacteria in the edema zone and prevent further spread. He noted⁴⁰ changes in the pneumococci in the edema zone suggesting bacteriostasis 18 hours after start of sulfa therapy. Forty-two hours after treatment the edema zone was gone, the pneumonia no longer spreading, and non-antibody phagocytosis was occurring in the peripheral exudate. In four days no pneumococci could be demonstrated and after one week only macrophages were present in the clearing area of pneumonia.

THE CLINICAL COURSE OF UNCOMPLICATED PNEUMONIA

Typical lobar pneumococcal pneumonia may be preceded by signs and symptoms of an upper respiratory infection. It may present itself suddenly in an unsuspecting previously healthy person with an abrupt and unannounced teeth-rattling chill or a stabbing breath-catching chest pain. These initial symptoms are then closely followed by a rising fever to 103° to 105° F. The respiration often becomes labored, with the accessory muscles of respiration, even the alae nasa, being brought into action. The patient may become cyanotic. Subsequently herpes simplex may flourish on the face.

Examination reveals tachypnea and tachycardia. The chest and lungs may show but a few fine rales at the onset. Shortly, however, there is dullness to percussion and increased fremitus over the involved lobe(s) with limitation of the thoracic excursion. Breath sounds are usually diminished and at least some rales are audible. These are the findings in the phases of congestion and early red hepatization.

The sputum is at first often bloody or blood-streaked and then characteristically becomes rusty.

Later, as the disease progresses, the more typical findings of consolidation such as bronchial breath sounds and transmitted voice sounds (bronchophony and egophony) are found, along with those described above.

Of interest is the clinical fact that often there is a disparity between the x-ray picture of the lungs and the physical findings. One may, on occasion, find physical signs of consolidation with little or no x-ray evidence, or the opposite may occur with little or no physical findings present or detected to substantiate the historical and x-ray evidence of pneumonia.

The diagnosis is established by finding the pneumococcus in the sputum by Gram stain and/or culture. Blood culture may also confirm the diagnosis.

The untreated patient will display a fever of 103 or 104° F. with a

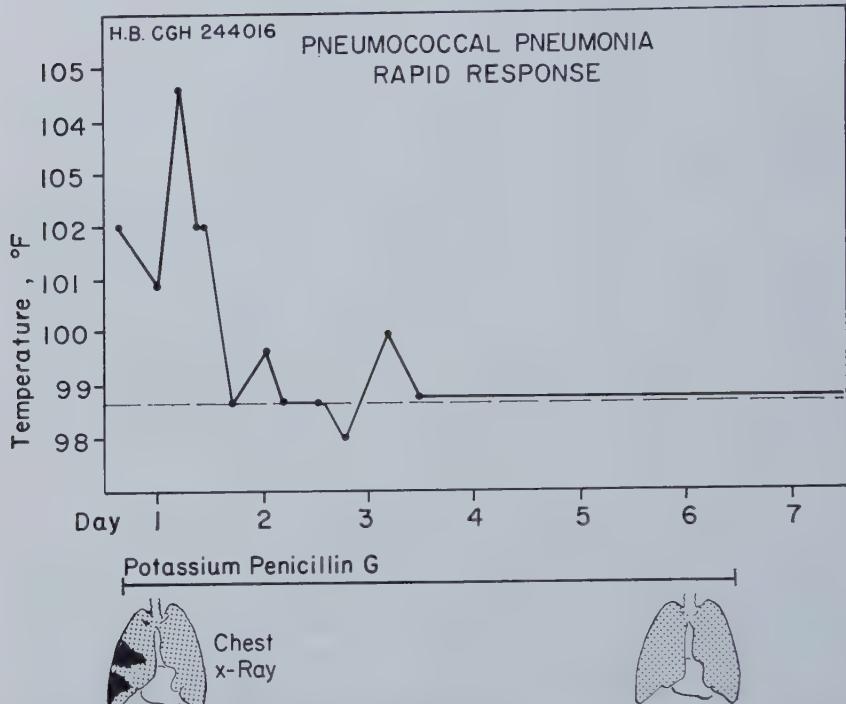


Fig. 1. This temperature chart illustrates a typical rapid response of a young otherwise healthy patient with pneumococcal pneumonia treated with penicillin.

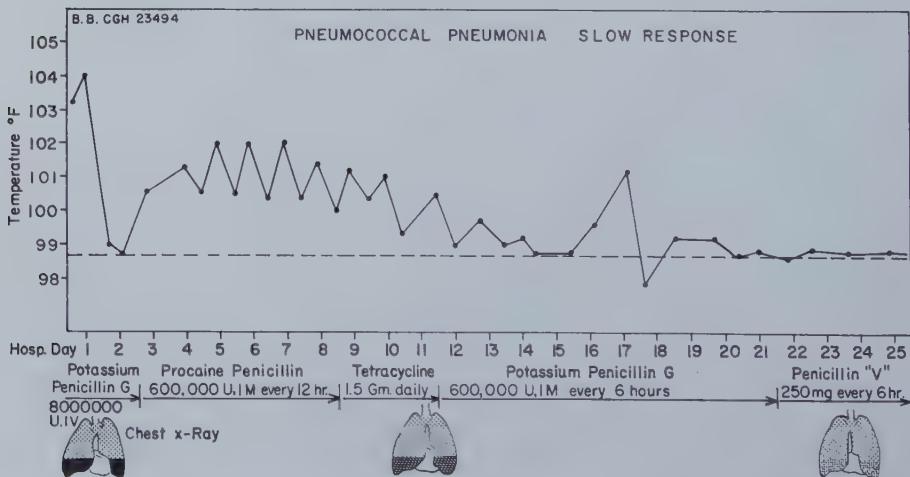


Fig. 2. This temperature chart illustrates a slow response of a patient with multilobe pneumococcal pneumonia. The initial high dosage and the subsequent alterations in the therapeutic regimen were not warranted by the slow uncomplicated response.

plateau-type fever curve for five to ten days. Then he may begin to improve either gradually with a slow decrease in fever and symptoms over a three or four day period (lysis) or there may be a sudden onset of perspiration and a rapid drop in temperature to normal or near normal levels within a few hours (crisis).

Twenty-five to 40 per cent of untreated patients have died of the disease in the past.

Specific treatment with either type-specific antibody or a bacteriostatic or bactericidal antimicrobial compound will usually alter the course of the disease by bringing about the onset of either lysis or crisis within a period of several hours of the administration of the treatment.

It has been our experience that house officers treating patients on the wards are often quite apprehensive when the properly treated patient does not experience a prompt crisis. We therefore should like to point out that a very slow lysis is often the clinical picture. A delayed response is not in itself an indication for altering the treatment schedule. (See Figs. 1 and 2.)

DIFFERENTIAL DIAGNOSIS

Pulmonary infarction is often difficult to differentiate from pneumococcal pneumonia. The patient may have a sudden onset of chest pain, dyspnea, fever and cough with hemoptysis. Chilling is unusual. The absence of pneumococci in the sputum and the presence of a site of origin for an embolus such as a phlebothrombosis in the leg or pelvis, or a possible thrombus in the heart either secondary to a myocardial infarction or auricular fibrillation would direct one toward a diagnosis of pulmonary infarct.

Sudden or transient evidence of pulmonary hypertension on the electrocardiogram or an increase in the pulmonary closure sound is also evidence of possible pulmonary embolus.

Certain findings on the chest x-ray also suggest the diagnosis of infarction such as a left pleural effusion with an enlarged heart, triangular or wedge-shaped infiltrates with the base on a pleural surface and the typical "Hampton's hump" in or near the costophrenic angle.¹¹

A major problem in differential diagnosis is that of deciding the etiologic agent of the pneumonia. Probably the most difficult decision is whether or not a severely ill patient has *Klebsiella pneumonia*. If there are encapsulated gram-negative rods on the smear of the patient's sputum, or if the severely ill patient has a chest x-ray picture with the typical "cannon ball" appearance or bulging fissure sign¹¹ so often associated with *Klebsiella pneumonia*, then a tentative diagnosis of this disease should be made and proper treatment instituted immediately. This should consist of tetracycline, 500 mg. every six hours, plus streptomycin, 1.0 gm. intramuscularly twice daily, and a sulfonamide, 4 to 6 gm. per day.²¹ If sensitivity studies prove the *Klebsiella* to be resistant to tetracycline, chloramphenicol, 500 mg. every six hours, should be given in place of the tetracycline.

Staphylococcal pneumonia is often seen, occurring in the public at

large as a sequela of influenza and occasionally arising as a complication of a treatment given a hospitalized patient. The diagnosis is often suggested by the x-ray appearance of the disease; for example, the pneumatocele is frequently seen or there may be early abscess formation. The sputum smear and culture should establish the diagnosis. Treatment may be given with methicillin, 1 gm. every six hours intramuscularly, plus probenecid, 0.5 gm. every six hours by mouth. If the patient cannot tolerate penicillin, vancomycin, novobiocin or chloramphenicol may be given. Sensitivity studies are often of great help in the treatment of staphylococcal pneumonia, particularly in hospital infections where various resistance patterns may occur in the staphylococci.

Tuberculosis, particularly the fulminating type, may be difficult to distinguish from lobar pneumonia by history, physical examination and x-ray studies of the chest. Often pneumococci are found in the sputum. However, the lack of clinical response and a Ziehl-Neelsen stain of the sputum will usually lead to the correct diagnosis.

When the clinical diagnosis is not readily made and good sputum is not obtainable, bronchoscopic examination and aspiration of bronchial secretions for smear and culture often demonstrate the etiologic agents. With frank consolidation, in selected patients needle lung puncture may be of value to obtain material directly from the diseased area for culture.

Any patient with pneumonia should be a *tumor* suspect. If the patient does not respond to treatment properly and if clearing of the infiltrate is not complete by x-ray within a period of four to six weeks, then evaluation for possible bronchial neoplasm or other forms of partial or complete obstruction should be seriously considered.

THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA

Historical Background

Two or 3 million years, more or less, probably passed from the time the first man or woman died of pneumococcal pneumonia until finally in the 1930's the use of type-specific antiserum became the widely recognized specific treatment of this disease.⁶ Prior to this great development, various and sundry remedies had been tried to no appreciable avail. Certain symptomatic and supportive measures were used which may have favorably influenced the death rate. Among these were the use of oxygen to relieve the cyanosis and improve respiration; intravenous and/or subcutaneous saline and glucose solutions; digitalis for the patients with heart failure and certain cardiac arrhythmias; codeine or morphine for the relief of pain and the exhausting cough. Even so, the death rate for pneumococcal pneumonia was often 40 per cent or higher.

Treatment of lobar pneumonia with type-specific antipneumococcal serum in the latter 1930's brought about a reduction of the mortality to about one-half its previous rate. Two large series of cases from the Boston City¹² and Cincinnati General Hospitals³² showed the death rate to drop from about 43 per cent to 22.6 per cent and 28.1 per cent respectively with this form of therapy.

Type-specific antiserum therapy was widely accepted and improvements in the serum and the therapy methods were occurring rapidly when sulfapyridine was introduced in 1938 as a new treatment of pneumococcal pneumonia.¹⁰

Later, other more soluble compounds such as sulfathiazole and sulfadiazine

were administered. These chemotherapeutic agents were found to be easier to administer to the patient than the antisera and did not require the determination of the exact type of infecting pneumococcus. Treatment of lobar pneumonia with sulfa compounds brought about a further decrease in the death rate to 15 to 20 per cent in Cincinnati,³² 17.5 per cent in Boston¹² and even 7.2 per cent in Baltimore.²²

The sulfa drugs remained the treatment of choice for pneumococcal pneumonia until 1944, at which time penicillin emerged as the most efficacious treatment to date.

Sir Alexander Fleming¹⁴ had originally noted the antibacterial activity of the Penicillium mold and labeled it penicillin in 1929. In 1940 a group of British investigators, Chain, Florey et al.⁵ used the substance to treat infected mice. They found penicillin to be nontoxic and active *in vivo* against at least three organisms, *Staphylococcus aureus*, *Clostridium septique* and streptococci. In 1941 the same laboratory¹ reported use of penicillin intravenously in the treatment of staphylococcal and streptococcal infections. They also used penicillin locally in the eye with good results. This group demonstrated how penicillin could be produced in quantity.

Tillett and his group in 1943³³ reported on the ability of penicillin to protect mice from infection with sulfadiazine-resistant pneumococci. Then in 1944 Tillett, Cambier and McCormack³⁴ reported the treatment of 46 cases of pneumococcal pneumonia with penicillin. There were only 3 deaths in this series, a mortality rate of but 6.5 per cent. In addition, this same group of authors successfully treated 7 of 8 cases of empyema by needle thoracentesis drainage and local instillation of penicillin into the empyema space. Thus, the modern era of treatment of pneumococcal pneumonia was launched.

As they have been discovered and produced, the newer antibiotics have been tried as treatment of pneumococcal pneumonia and many have been found to be satisfactory. Among these are erythromycin,²⁰ chlortetracycline, chloramphenicol and oxytetracycline.^{7, 35}

Variations in Penicillin Therapy

In the original 46 cases of pneumococcal pneumonia treated with penicillin in 1944 by Tillett et al.,³⁴ an aqueous solution of penicillin was used. This was administered intravenously or intramuscularly on a dosage schedule of 10,000 to 25,000 units every three hours for one to four days. Thirty-nine of the 46 patients had a rapid crisis in 10 to 20 hours after the start of therapy. It was noted that relapse was liable to occur if treatment was not carried out longer than two days. They also found that an interval of 12 to 16 hours between doses could be allowed. They therefore recommended that pneumococcal pneumonia patients be treated with four injections of 10,000 to 25,000 units of penicillin every three hours during the day time for three to four successive days.

During the past almost 20 years, the route of administration, the chemical nature of penicillin used, the amount of drug and the time interval between doses have been varied. In spite of these minor improvements there really has been no great change in the treatment of the disease or in the overall mortality rate.

The routine use of penicillin in the treatment of infections from 1944 to 1948 consisted of injections of the drug in amounts of approximately 25,000 to 50,000 units every three hours. In 1948 Altemeier² reported the satisfactory use of injection of 100,000 units of aqueous penicillin every

eight hours for the treatment of various infections seen on the surgical wards of the Cincinnati General Hospital.

Other investigators^{9, 31} found that more widely spaced injections of penicillin resulted in satisfactory treatment of infections. They postulated that continuous high blood levels were not necessary and hypothesized that it was important to allow some bacterial growth so that penicillin would be able to act.

During the winter of 1947-1948, Hamburger et al.¹⁶ treated 64 cases of pneumococcal pneumonia using a regimen of 300,000 or 200,000 units of aqueous potassium penicillin G intramuscularly twice in the first 24 hours and then once each day for six days or until the temperature was normal for 48 hours. This schedule of treatment resulted in a new low death rate of 6.3 per cent for pneumococcal pneumonia at the Cincinnati General Hospital.

Thus, the treatment of pneumococcal pneumonia evolved to that consisting of widely spaced injections every six to 12 hours, of relatively high doses, of 200,000 to 600,000 units of potassium penicillin G. However, even in the early days of penicillin treatment investigators were interested in the possibility of the oral use of the drug. Bunn, McDermott et al.⁴ successfully treated 44 of 45 cases with oral penicillin G, utilizing a dosage schedule of 200,000 units for the first dose and 50,000 units every two hours thereafter until 24 to 36 hours after the crisis, then 50,000 units every two hours from 8:00 A.M. to 10:00 P.M. The total treatment lasted four to seven days.

The same laboratory²⁴ a short time later reported on experimental observations concerning the metabolic fate of oral penicillin. They found that most penicillin was absorbed from the duodenum. Of that not absorbed, usually only a small amount was inactivated in the stomach and most was excreted in the stool or inactivated by bacteria in the colon. The absorption of penicillin was found to be rapid with maximum blood levels occurring in 30 to 60 minutes. Subsequently persisting blood levels were a reflection of the original maximum blood level and not the result of continued absorption. They felt that the requirement of larger amounts of penicillin when administered orally was a result of inadequate absorption and not inactivation by acid or bacteria.

In 1947 Dowling et al.⁸ treated two groups of pneumonia patients, one with 75,000 units of sodium penicillin buffered with calcium carbonate by mouth every three hours and another group with 15,000 units of crystalline penicillin G intramuscularly every three hours. There was no demonstrable difference in the results of the two types of treatment. The conclusion was that oral penicillin was an adequate treatment but should not be used for severe infections or when cost was a factor, but might be used when intramuscular injections were not feasible, as in the home treatment of pneumonia. Large oral doses five times the usual intramuscular doses were recommended.

Later other penicillin compounds were developed for oral use which did not need to be given as often because of better absorption and high blood levels. For instance, Harvey and Mirick¹⁸ used aluminum penicillin, 300,000 units by mouth every 12 hours successfully in 37 patients.

The drug was given until the patient was afebrile for 72 hours. Austrian and Winston in 1956³ used penicillin V (phenoxyethyl penicillin) 400,000 units every 12 hours. This preparation was found to be resistant to gastric acid and better absorbed from the intestinal tract. Seventy-three patients were satisfactorily treated in the mild to moderately severe pneumonia group.

At the Cincinnati General Hospital,^{25, 26} oral penicillin V was used for the treatment of moderate and severe pneumococcal pneumonia over a period of three years, 1955-1958. A total of 145 patients were treated, 94.4 per cent satisfactorily. The usual dose was 250 mg. every six hours. This form of therapy was considered to be safe and adequate for the great majority of patients with pneumococcal pneumonia but was not recommended for use in critically ill patients or those with purulent complications.

Modern Treatment

The treatment of pneumococcal pneumonia¹⁵ may be divided into two aspects, the extremely important supportive measures and the specific antibiotic treatment. Supportive treatment begins with bed rest; even those with mild disease should probably be in bed for the first two days. All patients should be at bed rest for two to four days and longer, if necessary, for abatement of the toxic phase. The diet is usually one of liquids for the first day or two, with progression to a regular diet as the patient is able to tolerate it. Fluid intake should amount to at least 3000 ml. per day, by mouth if possible. If the patient is not able to drink, intravenous fluids should be given. It is our usual practice to give 500 to 1000 cc. of 5 per cent glucose in normal saline and the rest as 5 per cent glucose in water. Oxygen should be used when there is even faint cyanosis and may be given to help relieve the dyspnea even when cyanosis is not perceived. Probably the best method of administration of the oxygen is by nasal catheter inserted to the level of the uvula in the posterior pharynx. The optimum oxygen flow rate is about 6 liters per minute. The pain of pleurisy may be relieved by 30 or 60 mg. of codeine but if this is not sufficient we do not hesitate to give the patient morphine, gr. $\frac{1}{6}$ to $\frac{1}{4}$, or 50 to 100 mg. of merperidine hydrochloride.

High fever, particularly temperatures of 104 to 105°, may be relieved by 0.3-0.6 gm. of aspirin. This, as well as a cooling sponge bath, often not only relieves the high fever but results in a more comfortable patient.

Antibiotic therapy for the moderately as well as the severely ill patient may now consist of phenoxyethyl penicillin (penicillin V), 250 mg. orally every six hours. If the patient is unable to take or retain oral medications for some reason, or if he is critically ill, then potassium penicillin G, 500,000 units, should be given intramuscularly every eight hours. This dose of penicillin should be regarded as maximum. It is sufficiently higher than proved effective schedules to provide a comfortable margin of therapeutic safety, yet probably not so high as to promote superinfection.

If the patient is unable to take penicillin because of sensitivity to the drug, then one of the proven adequate alternative treatments may be

prescribed. The patient may be given erythromycin, 250 mg. every six hours by mouth, or erythromycin glucoheptonate intravenously, 250 mg. every six hours. Tetracycline may also be given, preferably 500 mg. by mouth every six hours.

Antibiotic therapy should be continued until the temperature remains normal for at least two days.

There are other perfectly satisfactory antibiotic regimens which may be used in the treatment of pneumococcal pneumonia. There are some regimens which do not seem at all warranted, such as the use of multiple antibiotics. Chloramphenicol should not be needed, nor should the new antistaphylococcal penicillins. In an emergency room practice where large numbers of patients with pneumonia are treated, they are sometimes given an injection consisting of 1.2 million units of benzathine penicillin G and 600,000 units of potassium penicillin G, and follow-up care in the outpatient clinic where they may or may not be given further antibiotic therapy. This type of schedule is often adequate. However, Walker and Hamburger³⁶ treated 49 patients with a single injection of 600,000 or 1,200,000 units of benzathine penicillin G. The treatment was satisfactory in only 73.4 per cent of the cases and thus is not recommended for routine use.

COMMONLY ENCOUNTERED COMPLICATIONS

Sterile effusions are not infrequently seen in the course of pneumococcal pneumonia. The problem is to differentiate such an effusion from an early *empyema*. If there is no fever and no dyspnea, perhaps no treatment is necessary. If there is dyspnea, removal of enough fluid to relieve the dyspnea is in order. In massive effusions 1000 to 1200 cc. may be removed if the patient tolerates the procedure. Removal of fluid should also be done for diagnostic purposes, particularly if there is fever. The fluid should be examined for specific gravity, total protein, cell count and differential. A Gram stain as well as bacteriologic cultures should also be done. If there is any question of tumor, a portion of the fluid should be promptly preserved in formalin and tumor cell studies performed.

It is our opinion that whenever fluid is removed from the chest of a pneumonia patient, irrespective of whether it is grossly clear and suggests the presence of a sterile effusion or is grossly purulent and suggests empyema, penicillin or other antibiotic of choice for the particular patient should be instilled into the pleural space. If penicillin is used, 50,000 to 100,000 units of potassium penicillin G dissolved in 100 ml. of water is sufficient for instillation. A sterile effusion will resolve spontaneously as the patient improves.

If the patient has an empyema there will most often be a secondary rise in body temperature. The fluid when aspirated will be of high turbidity, with a specific gravity over 1.015. The total protein content will be 3.0 gm. or more. The white blood cell count will be elevated and consist mainly of polymorphonuclear leukocytes. Gram stain of the fluid and culture will often identify the bacteria present.

It is our experience, as in the original group treated by Tillett et al.,³⁴

that most patients with empyema, if recognized and treated early, can be managed quite satisfactorily with needle thoracentesis for the drainage of the empyema and instillation of antibiotic. Frequently only one or two thoracenteses will be necessary. Occasionally multiple thoracenteses will be required every second or third day in order to control the empyema. Tube thoracotomy is seldom needed except when the empyema is located in a spot inaccessible to the needle, or if the repeated needle aspirations are not tolerated by the patient. There seems to be no need for rib resection in the treatment of empyema today except perhaps in the exceptional case.

The use of proteolytic enzymes may be necessary and of benefit in breaking down fibrin walls producing loculations of empyema fluid. Such enzymes also may help liquefy the thick, viscid detritus which occasionally interferes with adequate drainage.

Acute endocarditis and *meningitis* are both severe complications of pneumococcal pneumonia which require intensive therapy. We customarily recommend a regimen containing 12 million units of potassium penicillin G intramuscularly daily. The duration of therapy will vary with the patient but it should continue until the patient has been afebrile for a week and clinical evaluation suggests that the disease is controlled.

Arthritis and *sinusitis* are occasionally encountered as purulent complications. Penicillin therapy should be continued and the pus evacuated. The evacuation may be done by needle aspiration of joints involved. Penicillin should be instilled into the joint space at this time. Nasal sinus drainage may be facilitated by vasoconstricting nose drops or sprays and may need irrigation. Direct surgical approach may be required.

The combination of lobar pneumonia and *acute alcoholism* or *delirium tremens* is a particularly hazardous one. The antibiotic treatment should be the same as that for any pneumonia. The supportive care must be altered. Fluids of high glucose and vitamin content are recommended and adequate sedation is mandatory. In the past the use of 5 per cent ethyl alcohol intravenously was often necessary. Today use of tranquilizing drugs such as methaminodiazepoxide (Librium) or chlorpromazine (Thorazine) parenterally has largely replaced the need for alcohol or paraldehyde. For example, the patient with delirium tremens may be given 1000 cc. of 10 per cent glucose in water intravenously, to which has been added 100 mg. of thiamine. It has also been the practice to add 20 units of regular insulin. Twenty-five to 50 mg. of chlorpromazine or 100 mg. of methaminodiazepoxide is given intramuscularly. Peripheral vascular collapse may be treated with levarterenol, 8 mg. in 1000 cc. of intravenous fluids, or metaraminol, 100 mg. in a liter of intravenous fluids.

The patient with *toxic hepatitis* usually requires no particular management except the routine. However, adequate fluid, vitamin and glucose intake should be assured.

Drug reactions in the treatment of pneumococcal pneumonia consist mainly of reactions to penicillin. Simple urticaria may recede after withdrawal of the penicillin and no further treatment is needed. Pruritus may

be alleviated by use of an antihistamine drug and/or topical soothing lotions such as calamine. More severe serum sickness type reactions with urticaria, arthralgia and fever may be prolonged and respond only to the administration of cortisone. In any reaction the penicillin should be discontinued and replaced by another antibiotic such as erythromycin or retracycline.

PROGNOSIS

Treatment with antibiotics has lowered the death rate of pneumococcal pneumonia to what may be an irreducible low level.

It has been pointed out by others,^{19, 35} and we agree, that certain factors are associated with increased mortality. Age is certainly a factor, the mortality rate rising rapidly after the age of 60. Concomitant disease such as heart disease, malignancy (such as myeloma) and other chronic illnesses, particularly chronic lung disease, increase the mortality. Chronic alcoholism is associated with a higher mortality rate. The death rate also rises with an increasing number of lobes involved by the disease and with the presence of bacteremia or leukopenia. Another obvious factor in continued mortality due to pneumococcal pneumonia is delay in starting adequate and specific antibiotic therapy in adequate dosage.

SUMMARY

Pneumococcal lobar pneumonia is an acute inflammatory disease of the lung, the nature of which has been extensively studied and described. The disease is spread peripherally by edema fluid carrying large numbers of pneumococci. The fluid moves from alveoli via the bronchi or the pores of Kohn. The body's main defense is phagocytosis of the bacteria by leukocytes and macrophages. The phagocytosis is augmented by the production of antibodies; however, this immune response may not occur until the patient is well on the way to recovery. The production of antibodies may occur some time before, or they may first appear at the time of onset of clinical recovery.

The administration of type-specific antibody results in an agglutination and opsonizing action of pneumococci in the edema zone with subsequent phagocytosis and obliteration of the zone.

Chemotherapy does not interfere with the immune response but helps prevent further spread of disease by bacteriostasis.

Treatment of pneumococcal pneumonia has evolved rapidly in the past 30 years from symptomatic treatment to type-specific antiserum to sulfa drugs and finally penicillin. Penicillin therapy has been improved and modified as far as dosage and method of administration are concerned but in recent years the mortality rate seems to be on a plateau and suggests that penicillin has reduced the mortality from pneumonia *per se* to its lowest achievable level.

Complications arise in the management of pneumonia. Most often they are of a purulent nature in the pleural space, joints or sinuses and require

drainage and antibiotic treatment. Endocarditis and meningitis require intensive, high-dosage antibiotic therapy. Other factors complicating the disease picture such as alcoholism, hepatitis and drug reactions require their own specific management measures.

The prognosis depends in large measure on the complicating or extenuating circumstances encountered. Thus the mortality rate has been found to be elevated by increased age, concomitant disease, multilobar involvement, bacteremia, leukopenia and delay in the initiation of treatment. The young, otherwise healthy patient who suffers from one lobe pneumonia is more likely to have a rapid clinical response than is the elderly patient with involvement of one or more lobes. Those patients with the complicating factors listed above seem more likely to have a delayed clinical response.

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Modern Drug Treatment of Mycobacterial Diseases

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BASIC PRINCIPLES

TUBERCULOSIS is usually a chronic disease characterized by lesions which undergo necrosis and cavity formation. Healing is accomplished mainly by fibrosis, calcification and scarring. Because of the relatively slow multiplication of the causative organism, the nature of the tissue reaction, and the leisurely pace of the healing process, chemotherapy must be given for prolonged periods and is usually not eradication. The various factors related to host resistance are important in determining the outcome. Microbial resistance is a dominant consideration because of the necessity for prolonged treatment and the very large population of organisms present in the lining of pulmonary cavities.

Indications for Treatment

The presence of active tuberculous disease is indication for treatment. The diagnosis of active tuberculosis may be suggested strongly on clinical grounds and supported by the radiographic appearance, but in every case vigorous attempts should be made to demonstrate acid-fast bacilli by smears and cultures before treatment is started. Rarely, it is necessary to resort to a therapeutic trial of antituberculosis drugs to help in establishing the diagnosis when other methods have failed, and in patients with suspected tuberculous meningitis it is often expedient to begin therapy immediately despite the absence of acid-fast bacilli in the spinal fluid.

Drugs may be used also in the prevention of tuberculosis. Primary prophylaxis, or the administration of drugs to prevent infection in individuals with negative tuberculin tests who are forced to live in a tuberculous environment, is being investigated on a large scale by the Public Health Service,⁹ with apparent success. Another type of prophylaxis, called "secondary," was proved to be useful in a study completed in 1961.¹⁴ The extrapulmonary complications of asymptomatic primary tuberculosis were largely prevented by the administration of isoniazid

to a group of young children who had positive tuberculin tests with or without radiographic changes.

It is now common practice to treat all children up to the age of four years who have a positive tuberculin skin test.

Combined Therapy

When patients with cavitary pulmonary tuberculosis were treated with streptomycin alone, an initial period of improvement was often followed by a relapse of the disease associated with the emergence of streptomycin-resistant bacilli in the sputum. In 1949 it was demonstrated that the emergence of streptomycin-resistant bacilli could be delayed by the simultaneous administration of PAS.⁶ A similar situation with regard to isoniazid resistant strains was recognized,¹⁹ and comparable delay was noted when PAS or streptomycin was given with the isoniazid. Thus, it became firmly established that combined therapy was necessary in the treatment of tuberculosis. Certain exceptions to this rule will be mentioned.

CHEMISTRY, PHARMACOLOGY AND TOXICITY OF DRUGS

Major Drugs

The big three in the chemotherapy of tuberculosis are isoniazid, streptomycin and para-aminosalicylic acid (PAS).

ISONIAZID is the generic name for isonicotinic acid hydrazide. Its structural formula is shown in Figure 1. It is absorbed rapidly and completely from the gastrointestinal tract and the concentration of active drug in the serum is roughly proportional to the amount administered. After a dose of 100 mg., a peak level of 1 to 4 mcg. per ml. appears in the serum at one to two hours, and this level falls gradually over the next four hours to an amount below detection. After 200 mg. the peak level is approximately 5 mcg. per ml. and at six hours it is 2. Much of the orally administered drug is metabolized to inactive compounds, mainly the acetyl derivative. It has been found that the fate of ingested isoniazid varies in different individuals. According to the rapidity with which the drug is metabolized, individuals may be grouped roughly into "rapid, slow and intermediate inactivators," depending on the serum concentration of active drug six hours after the oral administration of a test dose. Many studies have been done to determine the clinical significance of the rate of inactivation of isoniazid, but as yet no convincing evidence has been provided that the slow inactivators derive more benefit from the usual doses of isoniazid than the rapid inactivators. In this regard it also has been shown that the simultaneous administration of PAS may increase slightly the level of active isoniazid in the blood, presumably by interfering in some way with the excretion or the chemical alteration of isoniazid.

Isoniazid is widely distributed in all the body fluids and tissues. Levels in the cerebrospinal fluid are comparable to those in the blood. The drug is excreted rapidly predominantly by the kidneys. It may be given by

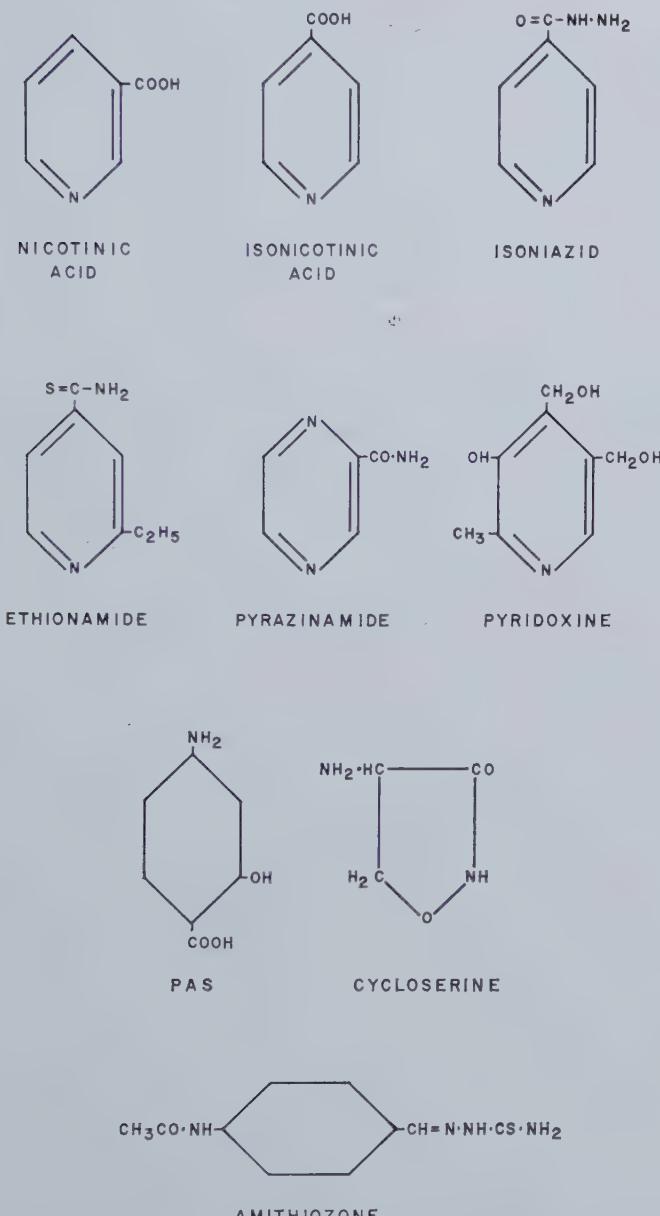


Fig. 1. Chemical structure of some antituberculosis drugs and related compounds.

the intramuscular or intravenous route if oral administration is not feasible.

Isoniazid is the least toxic of all the antituberculosis drugs. The most common complication is peripheral neuritis, and the chances of developing this compli-

cation are directly related to the dosage and the blood level of active drug. Rarely seen when 5 mg. per kg. per day is administered, its incidence increases progressively when larger amounts are given. It was pointed out by Biehl and Vilter¹ that the neuritis was due to disturbance in the metabolism of pyridoxine and that the administration of this vitamin will prevent the development of neuritis in patients given high dosage of isoniazid. In addition, a few cases of pellagra have been described during isoniazid therapy and these have responded to nicotinamide. Optic neuritis is rarely seen. Toxic psychosis has been described in a few patients. Apparently this effect is not related to dosage, and is not prevented by pyridoxine. Allergic reactions such as fever and skin rash are rare, but several cases of hepatitis presumably on an allergic basis have been noted.

STREPTOMYCIN is an antibiotic elaborated by *Streptomyces griseus*. Since it is very poorly absorbed from the gastrointestinal tract, the drug must be given parenterally. After intramuscular injection of 1 gm., a peak serum level of approximately 30 mcg. per ml. is achieved in one hour. This level falls rapidly until the fourth hour, then more slowly, and there is usually no detectable level after 12 hours. There is some variation in the blood level of active drug achieved by different individuals and in the metabolism and urinary excretion.³ Most of the streptomycin remains in the extracellular fluid compartment. It does not pass the blood-brain barrier readily, so that levels in the cerebrospinal fluid even in the presence of meningitis are usually not adequate. Its main pathway of excretion is through the kidneys.

Allergic reactions, mainly fever and skin rash and often accompanied by eosinophilia, occur in about 5 per cent of patients who are given streptomycin. The major toxic effect is damage to the vestibular and cochlear divisions of the eighth nerve. Directly related to total dosage, vestibular dysfunction may be expected in 10 to 20 per cent of patients treated with 1 gm. daily for over 3 months. Older people are at greater risk, probably because of inability to compensate for loss of vestibular function. Nerve deafness is noted much less frequently and is of later onset. It, too, occurs more often in older individuals, and in those with impaired renal function. At least partial recovery is the rule if the drug is discontinued promptly after the recognition of vestibular dysfunction, but the impairment of hearing is usually permanent and, indeed, may progress even after withdrawal of the drug.

Certain other effects on the nervous system have been observed. Toxic encephalopathy has occurred rarely, and then usually in patients who had excessively high blood levels because of impaired renal function. Paresthesias, especially around the mouth, are not uncommon soon after the injection. Evidences of renal irritation, such as the presence of casts and small amounts of albumin in the urine, are frequently observed, but usually are transient. In persons with previously damaged kidneys the use of full dosage of streptomycin may cause further dysfunction.

DIHYDROSTREPTOMYCIN is less toxic for the vestibular apparatus, but it is not recommended because of increased tendency to cause permanent deafness.

PARA-AMINOSALICYLIC ACID (PAS) is 2-hydroxy-4-aminobenzoic acid. Its structural formula is indicated in Figure 1. It is manufactured com-

mercially from m-aminophenol. The free acid is unstable and must be used within a few hours after mixing in aqueous solutions. The drug is usually administered as the sodium, potassium or calcium salt, since the salts are more stable, more soluble, and better tolerated. PAS is rapidly and more or less completely absorbed from the gastrointestinal tract, although the rate of absorption depends on the type of preparation used. When administered in aqueous solution, peak blood levels of approximately 100 mcg. per ml. appear in one to two hours, with very little measurable drug remaining after six hours. After the administration of PAS in tablet form absorption is delayed, peak levels are lower, and significant amounts remain in the blood for a longer time.

The drug is widely distributed in the tissues and body fluids and it is excreted mainly in the urine. Significant amounts can also be found in the feces. PAS is extensively metabolized in the body primarily by acetylation but also by conjugation with glycine and by other mechanisms.

With a rate of 7 per cent, PAS is the most likely of all the antituberculosis drugs to produce allergic reactions. A picture similar to that seen in infectious mononucleosis was described by Cannemyer et al.⁴ in 14 out of 5000 patients. In addition, a few cases of allergic pneumonia accompanied by eosinophilia have been described. Hepatitis, probably on an allergic rather than a toxic basis, is a more serious reaction which demands withdrawal of the drug. In one series it was found in 0.2 per cent of patients.⁵

The most troublesome side effects from PAS administration are related to gastrointestinal irritation. Almost everybody who takes the drug experiences some degree of anorexia and nausea. In some individuals the symptoms progress to vomiting and diarrhea of various degrees of severity. These manifestations can usually be controlled by experimenting with different preparations of the drug and by strong moral support on the part of the physician.

PAS can inhibit the binding of iodine in the synthesis of thyroid hormone. Rarely seen when the drug is given in the usual dosage, goiter occurs commonly when 20 gm. a day are ingested for prolonged periods.¹⁵

PAS has little bactericidal effect on tubercle bacilli in vitro, and, when used alone, only slight effect on tuberculous disease in animals and man.

Second Line Drugs

In this category are included those drugs which have been found to be most useful in the treatment of patients who for one reason or another were not able to derive benefit from the three major drugs. They are cycloserine, pyrazinamide, viomycin and ethionamide.

CYCLOSERINE is an antibiotic elaborated by *Streptomyces orchidaceus*. Chemically, the drug is D-4-amino-3-isoxazolidone (see Fig. 1). It is rapidly absorbed from the gastrointestinal tract so that peak levels in the blood appear within three to four hours and insignificant amounts remain at 12 hours. Approximately 35 per cent of the drug is chemically altered in the body to derivatives not yet identified. It is excreted primarily by the kidneys at a relatively slow rate. Cycloserine is widely distributed throughout the body fluids and it passes readily across the blood-brain barrier.

Allergic reactions and other side effects are rarely seen. The major toxic manifestations are related to the central nervous system and include somnolence, convulsions and psychosis. They are directly related to dosage and blood levels. On a dosage of 500 mg. twice daily, from 5 to 10 per cent of patients will have convulsions; the incidence may be reduced to 1 per cent by halving the dose.²⁰ Excessive alcohol intake and simultaneous administration of isoniazid increase the likelihood of convulsions.

PYRAZINAMIDE is a synthetic compound whose structural formula is shown in Figure 1. An analogue of nicotinamide, it also is similar structurally to isoniazid. It is readily absorbed from the gastrointestinal tract with a wide distribution throughout the body. Peak blood levels are reached approximately two hours after ingestion and the drug is excreted largely through the kidneys. A peculiarity of this drug is the lack of effect on mycobacteria other than human tubercle bacilli and the necessity for an acidic environment to demonstrate inhibition of growth.

Yeager²⁴ noted that patients treated with pyrazinamide alone often showed a temporary good response, followed by relapse of disease after three to six weeks. These early relapses are related to the emergence of drug-resistant bacilli. The greatest usefulness of the drug lies in the preparation for surgery of patients who have bacilli resistant to the major drugs. In this situation, especially when given with companion drugs, its relatively short-term but sometimes striking benefit best can be utilized.

The major drawback of pyrazinamide is liver toxicity. Approximately 15 per cent of patients receiving a full oral dose of 3 grams per day will develop signs and symptoms of hepatotoxicity, and 2 to 3 per cent may show jaundice. Several deaths have been reported from liver necrosis. An annoying side effect is a reduction of urate clearance by the kidney and the subsequent appearance of gout. The incidence of hepatotoxicity can be reduced by decreasing the daily dosage to 1.5 grams, but this maneuver is accompanied by a corresponding decrease in antituberculosis effect.

VIOMYCIN is an antibiotic produced by a species of *Streptomyces*. It is given by intramuscular injection. It has about one-quarter of the antituberculosis effect of streptomycin in vitro and in the experimental animal, but it cannot be given in adequate dosage to humans because of excessive toxicity and side reactions. Allergic reactions are common. Renal toxicity is evidenced by frequent appearance of casts and albumin in the urine, elevation of the blood urea nitrogen, and electrolyte imbalances such as low potassium, calcium, phosphorus and chlorides, and a high carbon dioxide combining power. In addition, damage to the cochlear and vestibular divisions of the eighth nerve may occur. For these reasons, the drug is usually given in dosage of 2 gm. (1 gm. twice a day) intramuscularly twice weekly, and at this level it is fairly well tolerated.

ETHIONAMIDE is 2-ethyl-thioisonicotinamide. It is a substituted thioamide of isonicotinic acid. From the structural formulas shown in Figure 1 it may be seen that this compound is closely related to isoniazid. That its antituberculosis effect is probably dependent upon the

sulfur-containing radical is indicated by the fact that there is *in vitro* cross-resistance of mycobacteria between ethionamide and amithiozone but not between the former and isoniazid. A summary of experimental and clinical observations was recently published by Brouet, Rist and co-workers.^{2, 17}

Very little is known about the pharmacology and metabolic fate of ethionamide. After oral administration of 500 mg., the peak blood level is reached at about two to three hours, but it varies widely from unmeasurable to approximately 2.5 meg. per ml., with an average of 0.8 meg. This level is only slightly less at six and nine hours. These values may be compared with the amount of drug necessary to inhibit growth of mycobacteria: 0.4 meg. per ml. in liquid medium without serum and 1.2 with serum. Only a small amount of ethionamide can be found in the urine after oral administration. The drug passes readily into the cerebro-spinal fluid.

Side effects and toxicity are common. The most disturbing of these is severe gastrointestinal intolerance which is manifested by at least half of the patients who receive 1 gm. daily. Skin rashes, some of them severe, are frequently noted. Several well documented instances of hepatotoxicity, some with jaundice, have been reported. At least one case of peripheral neuritis has been noted. Mental depression is not uncommonly seen.

Third Line Drugs

In this category are placed those drugs which generally are used only in desperate cases because of limited effect and excessive toxicity. It also includes those agents which are still under investigation.

KANAMYCIN is an antibiotic closely related to neomycin with which it shares antibiotic activity and toxicity. It is given by intramuscular injection, usually in regimens of 1 or 2 gm. 2 or 3 times a week. Irreversible deafness will occur in a sizable proportion of patients who are given 1 gm. daily for prolonged periods.

AMITHIOZONE (thiacetazone in Great Britain) is 4-acetylaminobenzaldehyde thiosemicarbazone. The structural formula is indicated in Figure 1. Having been more or less abandoned because of excessive toxicity, it recently has been tried again in East Africa. In one report of a co-operative investigation with the collaboration of the British Medical Research Council,⁸ encouraging results were noted when the drug was combined with isoniazid in previously untreated patients, and it was found to be as effective as PAS in preventing the emergence of isoniazid-resistant bacilli. In another report from Africa, Grounds¹¹ found that the combination of amithiozone and streptomycin was not effective in patients whose organisms were resistant to isoniazid and PAS.

Amithiozone is given by mouth in dosage of 150 to 200 mg. per day. Even with these low doses, serious blood dyscrasias and hepatitis may be seen. Three cases of Stevens-Johnson syndrome with one death have also been reported.

ETHAMBUTOL is a synthetic crystalline compound which demonstrates anti-tuberculosis activity in the test tube and in experimental animals. Pilot studies in humans revealed a distressing incidence of peripheral and optic neuritis, and a rapid emergence of drug-resistant bacilli was seen in patients to whom ethambutol was given as a single drug. Evaluation of its possible usefulness must await further clinical trials.

CAPREOMYCIN is a new antibiotic elaborated by *Streptomyces capreolus*. It is effective *in vitro* and it shows no cross-resistance with streptomycin. The limited clinical trials so far completed showed that it is an effective drug without significant toxicity for man.

OXYTETRACYCLINE has been used to treat tuberculosis in humans with varying results. All three of the tetracycline drugs exhibit a slight inhibitory effect on the growth of tubercle bacilli and a limited deterrent effect can be elicited in experimental disease in animals.¹² Trials in humans showed that those individuals who were able to tolerate 2 to 4 gm. of oxytetracycline daily for prolonged periods derived some limited benefit, mainly in that microbial resistance to the companion drugs, streptomycin or isoniazid, was delayed. Evidence for benefit beyond this is not convincing.

DRUG REGIMENS FOR TREATMENT

Most of our knowledge of the relative effectiveness of various drug combinations in the treatment of tuberculosis has come from the large-scale co-operative programs of the Veterans Administration-Armed Forces and the Public Health Service in the U.S.A., and of the British Medical Research Council. From these extensive data the following facts clearly have emerged. (1) Isoniazid is the most effective of the anti-tuberculosis drugs now available. (2) With few exceptions, treatment with single drugs is not optimal. (3) The emergence of drug-resistant tubercle bacilli is a major catastrophe which can best be avoided by combined drug administration on a continual basis. (4) Drug therapy must be prolonged and uninterrupted. (5) In original treatment patients who take their drugs according to plan, over 90 per cent can be cured of their disease.

Regimens of Therapy for Initial Treatment

For previously untreated tuberculosis there are three regimens from which to choose: (1) daily isoniazid plus daily PAS; (2) daily isoniazid plus daily streptomycin; (3) triple therapy with isoniazid, streptomycin and PAS, each daily, for 6 to 12 weeks, followed by isoniazid plus PAS.

The choice among these three regimens depends on an evaluation of the following five factors: relative efficacy, ease of administration and patient acceptance, incidence of side effects, cost, and type and extent of disease.

In carefully controlled studies involving large numbers of patients in the Veterans Administration-Armed Forces co-operative study, no significant differences were noted in the results obtained with the use of the triple drug regimen as compared with isoniazid plus PAS. Studies done in Great Britain have indicated a slight superiority of isoniazid plus daily streptomycin over isoniazid plus PAS. As far as the second, third and fourth factors are concerned, there is little doubt that treatment employing the two orally administered drugs, isoniazid plus PAS, rates the premier position, and in this country it is the most popular drug regimen. The triple drug regimen is used routinely by some clinics, but the majority of physicians treating tuberculosis today reserve this regimen for instances of severe illness such as tuberculous meningitis and very far advanced pulmonary disease.

The use of isoniazid alone in the treatment of active disease should be avoided whenever possible. Although the results in patients with minimal pulmonary disease without cavitation are only slightly inferior to those of combined therapy, it seems undesirable to invite the risk to the individual and to the community of favoring the emergence of isoniazid-resistant strains. Isoniazid alone may be used effectively for primary and secondary prophylaxis and for the continuing second or third year of chemotherapy in those patients without residual cavitation who have shown a good result from the first one or two years of combined therapy.¹⁰

Regimens of Therapy for Re-treatment

An increasing proportion of individuals with active tuberculosis are recalcitrant patients whose disease has relapsed because of interruptions of treatment and refusal to follow instructions. In order to plan treatment for these cases and for those whose relapse was based on other factors, it is necessary to know the drug-susceptibility pattern of their strains of tubercle bacilli. Most of them will harbor strains resistant to one or more of the three major drugs and one must turn to the second and third line agents. A regimen of two or three drugs is chosen to include any of the major drugs to which the organisms are still susceptible, and one or two others. Until the susceptibilities are known, it is usually best to administer two drugs to which the patient has never been exposed. There is some evidence that the continued administration of isoniazid may be beneficial even if the bacilli show *in vitro* resistance to it.^{16, 22} The serum antimycobacterial inhibition test⁷ may be used to help in the choice of a combination of drugs that will have an inhibitory effect on the patient's organisms. Many different combinations of drugs have been tried, with varying success. Depending on the severity of illness and the amount of irreparable damage to the lung, from 25 to 50 per cent of the resistant re-treatment cases may be salvaged by the intelligent manipulation of available drugs and the judicious use of surgery.

Dosage

The dosage for each drug is indicated in Table 1. The optimum dosage and rhythm of administration of isoniazid is still not settled. Large-scale controlled studies have not shown enough benefit from the larger doses to warrant the increased risk of side effects or the increased cost of the pyridoxine which must be given to prevent neuritis. Recent evidence from the Madras trials¹⁰ suggests that, when isoniazid alone is used, large daily doses are more effective than small ones and that a single daily dose is more effective than the same amount given twice daily. Until the situation is clarified, it is recommended that isoniazid be given in a daily dosage of 300 to 400 mg, either once or twice daily and that the higher dosages (with pyridoxine) be used only for cases of meningitis and very far advanced disease.

Streptomycin should be given once daily for maximum effect, but twice or thrice weekly injections may be used for continuing long-term treatment. As a companion drug with isoniazid, anything less than daily administration at the start of therapy increases the rapidity of emergence of isoniazid-resistant bacilli.

Table 1. Dosage, Toxicity and Allergic Reactions for the Principal Antituberculosis Drugs

DRUG	DOSAGE			ROUTE	MAIN TOXICITY AND SIDE EFFECT	INCIDENCE OF ALLERGIC REACTIONS
	Usual mg./kg./d.	High gm./d. [†]	mg./kg./d.			
Isoniazid	5-8	0.3	10-20*	Oral	Peripheral neuritis	Rare
Streptomycin	10-15	1.0	25	I.M.	Vestibular and otic damage	6%
Para-aminosalicylic acid (PAS)	200	12.0	300	Oral	Gastrointestinal upset	7%
Cycloserine	10	0.75	30*	Oral	Convulsions and psychosis	Rare
Pyrazinamide	20	1.5	40	Oral	Hepatitis and gout	Rare
Viomycin	10	2.0	20	I.M.	Renal and 8th nerve damage	Common
Ethionamide	10	2 X wk. 1.0	20*	Oral	Hepatitis, mental depression, gastrointestinal upset	Common
Kanamycin	—	1.0	—	I.M.	Deafness and renal irritation	Rare
Amithiozone	—	3 X wk. 0.150	—	Oral	Blood dyscrasias and hepatitis	Common

* With pyridoxine.

† For adults; higher dosage on body weight basis usually used in children.

The decision of how much risk one is willing to take in giving the more toxic drugs to the limit of tolerance will depend upon the seriousness of the patient's disease. If it is necessary to persist with a drug after minor allergic manifestations have appeared, one may try desensitization starting with minute amounts and gradually building up the dosage over a period of several weeks, or one may give large amounts of steroids for a few days and then rapidly increase the dosage of the drug. In many cases it is wiser to change to another agent.

Certain combinations of drugs seem to carry an increased risk of toxicity. For instance, central nervous system manifestations are more frequently seen with the combination of cycloserine and isoniazid than with either drug alone, especially when the dosage of isoniazid is high. The combination of pyrazinamide and ethionamide should be particularly dangerous since each drug is hepatotoxic.

Children seem to tolerate relatively large amounts of the antituberculosis drugs without difficulty. It is common practice to give them 10 to 20 mg. per kg. per day of isoniazid without pyridoxine. Damage to the eighth nerve by streptomycin is less often seen in children and they rarely exhibit reactions to cycloserine.

Duration of Treatment

The duration of drug treatment necessary to insure a good result depends upon such diverse factors as age, location and extent of disease, nature of the tissue reaction, and host resistance. Since one cannot assess accurately all of these factors, it is necessary to treat all cases for a long time in order to keep the relapse rate at a minimum. One year is the

minimum duration of therapy for prophylactic purposes; 18 months for active minimal disease; two years for the average case of moderately advanced disease; three years and more for very far advanced disease and in those who are left with thin-walled pulmonary cavities and repeatedly negative cultures of the sputum (the so-called "open negative syndrome"). In the case of older people who have fibrotic disease it has been recommended that isoniazid be given indefinitely, either alone or in combination with another drug.

Corticosteroids

There is no convincing evidence that the benefits gained by the administration of steroids in the average case of tuberculosis outweigh the potentially harmful side effects. Controlled studies have shown that, during the first three months of treatment, there is usually a more rapid defervescence of fever, more rapid weight gain, and an increased rapidity of radiographic clearing, but cavity closure, sputum bacteriology and degree of physiologic damage two to three years later are not affected. It must be realized, however, that when steroid therapy is indicated for other reasons (adrenal insufficiency, lupus erythematosus, etc.) it may be given to patients with tuberculosis under cover of effective chemotherapy.

From the evidence available at this time the administration of steroids in tuberculosis is probably indicated under the following conditions: (1) in tuberculous meningitis, especially where there is evidence of cerebrospinal fluid block; (2) when the disease is so acute and fulminating that the "toxic state" is felt to be life-threatening; (3) to control serious allergic reactions; (4) to hasten clearing of the atelectatic-pneumonic pulmonary segments associated with primary tuberculosis in children, and to hasten absorption of pleural fluid.

DISEASES ASSOCIATED WITH OTHER MYCOBACTERIA

In addition to *M. tuberculosis*, mycobacteria of several other species and unnamed groups produce disease in man. The pathologic processes can vary widely from isolated, acute lung or subcutaneous abscesses to extensive involvement of the reticuloendothelial system, but the usual manifestations are either a chronic pulmonary process similar to tuberculosis or a subacute localized lymphadenitis.^{5, 18}

These mycobacterial diseases are more difficult to treat because the organisms are generally more resistant than *M. tuberculosis* to the antituberculosis drugs. Experience has shown that strains of *Mycobacterium kansasii* usually exhibit relatively greater sensitivity than do the other "atypical" mycobacteria.²³ In experimental infections of mice it was found that both isoniazid and streptomycin were partially effective and the combination of these two drugs slightly more beneficial than either alone.²¹ For the treatment of *M. kansasii* infections in humans it is recommended that isoniazid plus streptomycin be given, the former in high dosage of 10 to 15 mg. per kg. per day with pyridoxine, and the latter 1 gm. daily. If a third drug is needed because of a high degree of

in vitro resistance to isoniazid or streptomycin, it should be cycloserine, amithiozone or ethionamide.

For infections caused by other strains of atypical mycobacteria ("Battey" bacilli, scotochromogens, *M. fortuitum*, etc.), chemotherapy is not satisfactory. The organisms usually exhibit strong resistance to isoniazid, although some have a fair degree of susceptibility to streptomycin. *In vitro* tests indicated that cycloserine inhibited the growth of most of these cultures, and that amithiozone was not as effective for them as it was for *M. kansasii*.²³ An occasional culture shows susceptibility to one or another of the antimicrobials active against pyogenic organisms. The best one can do, therefore, is to give triple therapy with high dosage of isoniazid, daily streptomycin, and another drug to which the organisms show *in vitro* susceptibility.

SUMMARY

Remarkable results can be obtained today in the initial therapy of active tuberculosis. When treatment is uninterrupted, prolonged, and combined (two or more effective drugs), a good result may be expected in over 90 per cent of patients. The most popular regimen today is isoniazid in moderate dosage plus PAS. Triple therapy with isoniazid, streptomycin and PAS for at least the first several weeks of treatment is recommended by some but is not clearly more beneficial for the vast majority of patients. Isoniazid alone is useful in prophylaxis, but is to be avoided in the treatment of active disease under ordinary circumstances.

Most of the therapeutic problems are encountered in the re-treatment of patients whose organisms are already resistant to one or more of the major drugs. Similar difficulties arise in the treatment of the patients who have been infected primarily with drug-resistant organisms acquired from unsuccessfully treated individuals, and in those infected with mycobacteria other than mammalian tubercle bacilli. In these situations one treats with a regimen of two or three drugs chosen with the aid of drug susceptibility tests of the patient's organisms, and using some of the second and third line agents.

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The Diagnosis and Treatment of Bacterial Endocarditis

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LIKE MANY of the diseases which have been clearly described and well recognized as clinical and pathologic entities in relatively recent times, bacterial endocarditis undoubtedly has affected man for centuries. Its precise characterization, however, awaited the development of the sciences of pathology and bacteriology; consequently, the disease has come to be well understood only during the past 100 years. Nonetheless, it was recognized as far back as the sixteenth century, and was of interest to a few physicians in the long intervening period when medical knowledge grew only slowly. An excellent summary of the history of this entity may be found in Kerr's monograph.⁴³

Bacterial endocarditis also represents an example of the remarkable progress which has marked medical therapy in the past three decades, particularly in the field of infectious diseases. For in this period, the application of the fruits of research to clinical medicine, in the form of agents with potent antimicrobial capability, has altered spectacularly the course and prognosis of many diseases of bacterial origin. In the case of bacterial endocarditis, a disease previously for all intents and purposes universally fatal, has been brought in large measure under effective control.

Bacterial endocarditis has occupied the interest of many distinguished clinicians including Osler,⁵⁷ Horder,³⁴ Schöttmuller,⁶⁹ Libman,⁴⁵ Blumer⁷ and Thayer,⁷⁴ and many excellent descriptions of the symptoms, signs and course of the disease have appeared in the literature.⁴⁶ Because of the lack of satisfactory therapy until the advent of the antibiotics, the many variations of the untreated disease have been well documented.

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Definition

Bacterial endocarditis is a disease characterized by infection of the surface of the valves or mural endocardium. The valves are much more frequently involved than is the mural endocardium, the latter being affected chiefly when endocarditis occurs as a complication of a ventricular septal defect or other congenital malformation. It should be noted that endocarditis may also be caused by higher organisms, in particular by fungi. Fungal endocarditis has been seen more frequently of late as a result of the alteration of the normal pattern of bacterial flora by antibiotics. This matter will be discussed briefly in a subsequent section.

In the older literature, endocarditis was usually divided into two forms, acute and subacute.⁴⁶ The division was based generally on temporal considerations. When the process was of short duration, i.e., less than six weeks, the term acute was applied. It was also not uncommon to use this term for the process when organisms other than nonhemolytic streptococci or *Streptococcus viridans*, e.g., beta hemolytic streptococci or pneumococci, were the causative bacteria. Not infrequently, when the therapy of acute pyogenic infection was ineffective, acute endocarditis arose as a complication of a suppurative process of extracardiac origin and apparently normal endocardium was involved.

In any case, it seems unnecessary to make such an arbitrary distinction in bacterial endocarditis. The disease is extremely protean in its manifestations, and may on occasion be characterized by a long, rather undramatic course. It seems preferable, therefore, to use the term bacterial endocarditis to describe the disease, substituting the causative organism, when it has been identified, for the word "bacterial."

Etiology

The majority of cases of bacterial endocarditis are due to streptococci of the nonhemolytic type, using this term to include various strains of *Streptococcus viridans* and the enterococci. In older series, between 90 and 95 per cent of patients afflicted with the disease were infected with one of the nonhemolytic streptococci; more recently, the emergence of penicillin-resistant staphylococci has brought this organism into prominence as the etiologic factor in many cases.⁴⁶ In addition, the common gram-negative rods have been responsible for a small number of infections^{47, 63} as have strains of brucella.¹³ Isolated instances of infection with a wide variety of bacteria have been recorded and occasionally mixed infection may occur.

As already noted, fungi may also be the causative organisms, especially in patients with debilitating diseases in whom long exposure to antimicrobial agents has taken place.

Pathogenesis

The pathogenesis of bacterial endocarditis is not completely defined although considerable information is available in respect to factors of importance. It is obvious that the presence of bacteria in the blood stream is essential to the development of bacterial endocarditis. A large body of evidence has substantiated the common occurrence of transient bacteremia, after such everyday procedures as teeth brushing or gum chewing.^{4, 54, 56} After minor dental procedures, and especially after extractions, the incidence and intensity of bacteremia are enhanced.²⁸ Most often the blood-borne organisms are nonhemolytic streptococci which normally inhabit the oral cavity. After manipulation of the

genitourinary tract, as in catheterization or cystoscopy,⁶⁰ or after normal deliveries,¹⁰ enterococcal as well as gram-negative bacteremia may occur.

When an underlying endocardial defect is present, or in congenital cardiac malformations, transient bacteremia constitutes a serious threat by virtue of the fact that the abnormal surface or structure may serve as a locus for the bacteria. Presumably the bacteria implant on the damaged or abnormal endocardial wall from the general blood stream,⁴¹ but it is possible that in the case of valves damaged by rheumatic fever the organisms may embolize the vascular channels which develop under such circumstances.³¹ The presence of platelet thrombi or other vegetative lesions serve as especially likely sites for bacterial implantation.³⁰ Once implanted, the bacteria tend to become enmeshed in fibrin which affords a matrix in which multiplication occurs. The fibrin also tends to protect the bacteria against certain antimicrobial agents, e.g., sulfonamides, which do not diffuse readily through fibrin.³²

Other Predisposing Factors

In addition to rheumatic valvular disease or congenital malformations, bacterial endocarditis occasionally occurs on aortic valves damaged by syphilis or atherosclerosis, and rarely on the endothelium of arteriovenous aneurysms resulting from trauma. In the latter instance, if treatment is delayed, the endocardium, though normal, may also become secondarily involved.¹²

Pathology

The hallmark of bacterial endocarditis, in terms of gross pathologic change, is the presence of an infected vegetation superimposed on a damaged valve. Often the vegetations are large, and they are usually friable, a fact which correlates with the high incidence of serious or even fatal embolization.

Characteristically the process involves the mitral or aortic valves. When the underlying lesion is a septal defect, the vegetation may develop on the endocardium of the right ventricle, opposite the defect. Vegetations may involve the chordae tendineae, and in advanced cases rupture of the chordae or perforation of an affected valve may take place, such events usually being marked by dramatic deteriorative changes in cardiac function.

Microscopically, the vegetations in untreated patients consist of masses of bacteria, polymorphonuclear and/or mononuclear leukocytes, erythrocytes and fibrin. Moore has described carefully the healing process in vegetations when an effective antimicrobial agent is given.⁵³

In untreated patients, the occurrence of emboli results in infarcts which often are noted in the kidneys, spleen and brain. Less often, mycotic aneurysms may develop when bacterial emboli localize in arterial walls.

SIGNS AND SYMPTOMS

The manifestations of bacterial endocarditis may be extremely variable; indeed, in given cases, the paucity of findings may obscure the fact that a serious disease process exists. In most instances, however, a number of clues are available. Included are one or more of the following nonspecific evidences of illness: fever, often with chills and night sweats, malaise, anorexia, pallor and anemia. As already stated, the presence of friable vegetations on the affected endocardial surface gives rise frequently to emboli which, in turn, depending on their size and ultimate localization, may be noted as petechiae in the skin or mucous membranes

or as splinter hemorrhages in the nailbeds. When the diagnosis of bacterial endocarditis is suspected, a careful search for petechiae is indicated, with special attention to the conjunctivae, the oral cavity and the optic fundi. Osler nodes, small painful lesions usually found on the palms or soles, and Janeway lesions, small, raised, nontender erythematous nodules, are typical of bacterial endocarditis.

Since emboli frequently lodge in the kidneys and the spleen, they may produce sudden pain in the appropriate region. In the case of renal involvement, focal embolic nephritis or infarcts are often noted, and hematuria is a common finding. When emboli occlude vessels in the brain, serious or even fatal neurologic defects may result. If endocarditis involves the right side of the heart, the lungs may be the site of tiny emboli, and diagnosis may be difficult.

Another manifestation of bacterial endocarditis, especially in advanced cases, is clubbing of the fingers.

The presence of a cardiac murmur, particularly in a febrile patient, should call attention to the possibility of endocarditis; when the murmur changes in character, the likelihood of bacterial endocarditis is enhanced.

LABORATORY FINDINGS

In addition to anemia of normocytic, normochromic type, there may be a moderate leukocytosis with left shift. The sedimentation rate is usually elevated. Albuminuria and hematuria are common.

The most important laboratory aid in the diagnosis of bacterial endocarditis is the blood culture. In at least 80 per cent of patients, positive blood cultures can be obtained, particularly if multiple samples of blood are obtained.^{9, 29} When substantiation of bacterial endocarditis is sought, at least five cultures should be drawn. Meticulous attention to technique is important; blood should be cultured both aerobically as well as anaerobically, and it must be remembered that certain bacteria may grow slowly. Consequently, cultures should be incubated for at least 15 to 20 days before being discarded. Fungi are more easily recovered when Sabouraud's agar is inoculated with blood.

DIAGNOSIS

Perhaps the single most important factor in the correct diagnosis of bacterial endocarditis is a high degree of suspicion on the part of the physician. In patients with either acquired valvular disease or congenital cardiovascular abnormalities, the presence of fever, with or without emboli, should call for vigorous attempts to confirm the diagnosis of bacterial endocarditis. It is imperative that multiple blood cultures be obtained promptly; if the evidence for a presumptive diagnosis is convincing, therapy should probably be begun as soon as five or more separate blood cultures have been drawn. Under these circumstances the choice of the most effective drug cannot be based on objective criteria, but large amounts of penicillin with streptomycin should be given while the results of blood cultures are awaited. In most instances, when bac-

terial endocarditis develops in a patient who has not been receiving antibiotics for other reasons, and in whom no other underlying medical problem has existed, the causative organism is statistically apt to be a nonhemolytic streptococcus, and in these circumstances the above therapy can be expected to be effective. As has already been emphasized, in patients subjected to long courses of antibiotics and in those who have had reparative cardiac surgical procedures, endocardial infection due to staphylococci or fungi has recently emerged as a major problem.

TREATMENT

The therapeutic challenge of bacterial endocarditis has undergone significant alteration in the past decade. The disease was for all practical purposes universally fatal until the introduction of the sulfonamides, with which a small percentage of cures was effected. The advent of penicillin therapy marked the onset of a new era, and a high cure rate of streptococcal endocarditis became attainable. More recently, however, the widespread and often indiscriminate use of penicillin and of broad-spectrum agents has resulted in a marked increase in endocarditis due to penicillin-resistant staphylococci and gram-negative rods. Many of these organisms are extremely difficult to eradicate.^{47, 59} Further, a new dimension has been added to the therapeutic problem of this disease by the rapidly increasing application of newer cardiovascular surgical techniques. Intravascular and intracardiac sutures, patches and prosthetic valves may act as foci of infection, and present a rigorous test of both the efficacy of therapeutic agents and the resourcefulness of the physician. Finally, the problem of fungal endocarditis, already alluded to, is significant.

While penicillin G, after 20 years of clinical use, has yet to be supplanted as the primary antibiotic for use in the treatment of bacterial endocarditis due to nonhemolytic streptococci and some strains of staphylococci, microbial resistance is becoming an ever-increasing problem. Two recently introduced drugs, methicillin and colistin, have to date shown considerable promise in the treatment of a variety of penicillin-resistant bacterial infections. The characteristics of these two antibiotics will briefly be reviewed.

New Antibiotics

Staphylococci resistant to penicillin G were recognized shortly after this antibiotic was first introduced, and the number of such strains has increased steadily so that they now account for 80 per cent of the serious infections caused by this species.¹ Penicillin resistance is due to an enzyme, penicillinase, elaborated by staphylococci; this substance hydrolyzes penicillin G at the beta-lactam ring, yielding an inactive penicilloic acid. Recently a new penicillin, sodium dimethoxyphenyl penicillin (methicillin), having the unique property of penicillinase resistance, has been synthesized. This antibiotic, therefore, is equally effective against both penicillin G-sensitive and resistant staphylococci.

Methicillin, however, should be reserved only for the treatment of penicillin G-resistant staphylococci since it exhibits only one-fiftieth the activity of the latter drug against sensitive staphylococci. Thus, to achieve an effect equivalent to 20 million units of penicillin G in a patient with a sensitive staphylococcal infection would require almost a kilogram of methicillin.

To date, only a few isolated incidences of coagulate-positive staphylococci resistant to methicillin have been reported;³⁷ it should be noted, however, that some strains of *S. albus* and most strains of enterococci are resistant to this antibiotic.^{70, 71, 76}

Methicillin is a nontoxic bactericidal agent, which like penicillin G, is active against multiplying cells. It must be administered parenterally, either by the intravenous or intramuscular routes, because its acid-lability absorption from the intestinal tract is inadequate. It is excreted by the kidneys and serum concentrations are elevated and prolonged by the concomitant administration of probenecid by mouth.⁶⁵ There is no contraindication to its use in the presence of renal impairment although relatively smaller doses will maintain therapeutic serum concentrations in the presence of azotemia.

The untoward reactions which have been attributed to methicillin include urticarial skin rashes, exfoliative dermatitis, drug fever, and neutropenia with elevation of the serum iron concentration.^{50, 84}

Colistimethate sodium (colistin) is a bactericidal polypeptide antibiotic composed of five amino acids. It has the same structure as polymyxin B except that it lacks a phenylalanine residue.¹⁹ This drug is active primarily against gram-negative rods, *E. coli*, pseudomonas, klebsiella, aerobacter and paracolons, but not proteus. As would be anticipated, there is cross resistance between colistin and polymyxin B. The intramuscular route is used for administration, for the drug is not absorbed from the gastrointestinal tract. Colistin is excreted by the kidneys and has been shown to be less nephrotoxic than polymyxin B.⁸⁵ While there is apparently no contraindication to the use of colistin in the presence of renal insufficiency, reduced dosages should be employed in azotemic patients.¹⁹ When colistin is administered to such patients, there may be an increase in azotemia while the drug is being given but return of the blood urea nitrogen to pretreatment levels may be expected after the antibiotic has been discontinued. Additional side effects include neurotoxicity with perioral numbness and tingling, other paresthesias, vertigo and pruritus.

Microbiologic Laboratory Determinations

In addition to the isolation and identification of the etiologic agent, two additional types of information can be supplied by the laboratory to aid the clinician in planning the treatment of patients suffering from endocarditis. These are as follows: (a) the *in vitro* antimicrobial sensitivity pattern of the infecting organism; and (b) the degree of inhibition of the organism by the patient's serum after antibiotic therapy has been started. The former points to the agent or agents most likely to be effective, and the latter, utilizing tube dilution

studies, may indicate that especially high doses of an antibiotic are required for a satisfactory therapeutic effect. They may point to particularly effective antibiotic combinations when the upper limits of drug dosage is fixed by intrinsic toxicity as, for example, with kanamycin.³⁷

In the case of the streptococci, it is useful to distinguish the penicillin sensitive (<0.1 units/ml.) strains from those showing only moderate sensitivity (0.2 units/ml. or greater). The more resistant strains distinctly call for administration of higher doses of penicillin over longer periods of time.

Streptomycin sensitivity studies of enterococci are usually of little importance. Even in those strains which show a marked degree of resistance to this antibiotic, it appears to exert a synergistic effect when given with penicillin and to enhance the killing of enterococci. Thus, even if either the tube dilution or disc plate techniques indicate streptomycin resistance up to 100 meg./ml., the drug should still be employed in therapy.^{36, 44, 78}

After antibiotic therapy has been instituted, it is useful to measure the inhibitory activity of the patient's serum against the infecting organism.^{22, 62} Determinations of both the greatest dilution that will inhibit growth (bacteriostatic level) and that which will kill the bacteria (bactericidal level) should be made. While it is desirable that the serum should be bacteriostatic in a dilution of 1:16 and bacterical at 1:4,⁵⁹ it must be remembered that these figures represent only a rough guide and will of necessity vary with the organism, the antibiotic, the site of infection and the size of the inoculum. Determination of serum antibiotic levels has value also in patients with renal insufficiency who are receiving a relatively toxic drug such as vancomycin, kanamycin or colistin, providing as it does a means whereby excess serum accumulation of the given antibiotic can be avoided.

Recommended Antibacterial Therapy

STAPHYLOCOCCI

Endocarditis due to penicillin-sensitive staphylococci can be effectively treated with 40 million units of aqueous crystalline penicillin G, given daily by the intravenous route for six weeks. Probenecid, 0.5 gm. every six hours, given orally, is a useful adjunct. Because of its synergistic effect against staphylococci when combined with penicillin, streptomycin should be administered in a dose of 0.5 gm. intramuscularly every 12 hours for the first three weeks, and then daily for the last three weeks.⁵⁵

As has already been noted, in the presence of renal insufficiency less penicillin is required to maintain adequate blood concentrations. It is also important to keep in mind the fact that one million units of aqueous penicillin G contains 1.6 mEq. of potassium.

In the treatment of endocarditis due to staphylococci resistant to penicillin G, methicillin, 2 to 6 gm. in 100 ml. of 5 per cent dextrose in water, should be infused intravenously over a 30 minute period every six hours for six weeks. While convincing evidence of synergism between streptomycin and methicillin has not been presented, it seems reasonable, on an empirical basis, to add the former to the therapeutic program if *in vitro* sensitivity is demonstrated. Probenecid should also be used because of its effect in increasing and prolonging the blood levels of methicillin.⁶⁵

If the clinical response of patients with endocarditis due to either penicillin G-sensitive or resistant strains of staphylococci is not satisfactory within two or three days, one of the following drugs should be added to the program, depending on the results of *in vitro* sensitivity studies: vancomycin, 1 gm. in 50 ml. of 5 per cent dextrose in water given intravenously over a 15 minute period every 12 hours for three weeks;²⁶ kanamycin, 0.5 gm. intramuscularly every 12 hours, for not more than 20 days of total therapy; or chloramphenicol, 1 gm. in 100 ml. of 5 per cent dextrose in water given intravenously over a 30 minute period every eight hours.

In the unlikely event that endocarditis is caused by one of the rare strains of methicillin-resistant staphylococci, vancomycin therapy is probably the drug of choice.

VIRIDANS STREPTOCOCCI, ALPHA-HEMOLYTIC STREPTOCOCCI AND ENTEROCOCCI

Streptococci of the viridans group, the so-called green or alpha hemolytic streptococci, are usually sensitive to less than 0.1 unit/ml. of penicillin G.^{16, 21, 80} Aqueous procaine penicillin in a dose of 600,000 million units intramuscularly every six hours for two weeks, probenecid 0.5 gm. orally every six hours, and streptomycin, 1 gm. intramuscularly every 12 hours for the first week and every 24 hours for the second week, should be administered to patients with endocarditis due to a strain of this organism. Hunter and Patterson³⁵ reviewed 146 patients treated in 23 different clinics and found that after only two weeks of therapy the relapse or failure rates were comparable to those reported for patients treated for longer periods.

Patients with endocarditis due to enterococci, or to streptococci requiring 0.2 units/ml. or more of penicillin G for inhibition, should receive 20 to 40 million units of aqueous penicillin G daily by the intravenous route for a period of six weeks. Probenecid, 0.5 gm. orally every six hours, and streptomycin, 1.0 gm. intramuscularly every 12 hours for the first three weeks and then daily for the second three weeks, are important therapeutic adjuncts. If the patient's response is not satisfactory, the penicillin dosage should be increased twofold or more.

Although not the preferred therapy, good results have been reported in the treatment of enterococcal endocarditis with ristocetin. One gram of this agent, given every 12 hours by rapid infusion for 14 days, was found to cure nine of ten patients.⁶⁶ Reactions to ristocetin including skin rashes, exfoliative dermatitis, ototoxicity, nephrotoxicity, neutropenia and thrombocytopenia are not infrequent.^{24, 66, 83}

GRAM-NEGATIVE BACILLI

In endocarditis due to the coli-aerogenes group, paracolons, proteus, pseudomonas and klebsiella species, experience dictates that the most favorable results are produced when a bactericidal agent, such as streptomycin, kanamycin or colistin plus a bacteriostatic drug, either chloramphenicol or one of the tetracyclines, is employed. The choice of antibiotics and specific combinations should be determined primarily by the

results of *in vitro* sensitivity studies on the causative organism. The duration of therapy should be at least six weeks.

When streptomycin is used, the optional dose is 1 gram intramuscularly every 12 hours. In the presence of renal insufficiency or when there is evidence of ototoxicity, the dose should be halved. Recommended kanamycin dosage is 0.5 gm. every 12 hours intramuscularly. The total dose should not exceed 20 gm. because of the likelihood of producing nerve deafness when larger amounts are given, and the dosage should be decreased in patients with oliguria. The tetracyclines and chloramphenicol may be given in 1 gm. amounts in 100 ml. of 5 per cent dextrose in water over a 30 minute period every six to 12 hours. Waisbren et al. reported that they had administered as much as 18 gm. of chloramphenicol intravenously in a 24 hour period, and that the addition of vitamin B₁₂ and folic acid apparently prevented glossitis.⁸² Bone marrow toxicity was not observed in their patients. The advisability of administration of these dosages, however, awaits further confirmation, and frequent monitoring of the white blood cell count is indicated in patients receiving chloramphenicol.

Pseudomonas endocarditis has been found to be particularly refractory to chemotherapy. Sykes et al.⁷² reviewed seventeen cases of this entity, not associated with cardiac surgery. Fourteen patients succumbed; in the three cases in which a favorable outcome was observed, neomycin was used in one, polymyxin B in the second and splenectomy was performed in the third and apparently led to cure. Currently, colistin seems to be the most promising drug for the treatment of endocardial infections due to *pseudomonas*. Doses of 150 mg. intramuscularly every 12 hours should be used, and on the basis of the potentiating effect exhibited by oxytetracycline when it is given with polymyxin B, it is suggested that the former agent may also be a useful adjunct to colistin therapy.⁸¹ Mixed endocarditis due to *pseudomonas*, *staphylococcus* and *candida* species have been reported;⁵⁹ needless to say, the treatment of this type of infection is an overwhelming problem for even the most resourceful clinician.

Indol-negative *proteus* strains such as *Proteus mirabilis* are often sensitive to massive doses of penicillin G, and therapy including 40 to 60 million units of penicillin, combined with a second antibiotic, selected on the basis of *in vitro* sensitivity tests, and probenecid may be expected to result in cure.

CULTURE-NEGATIVE ENDOCARDITIS

In 10 to 20 per cent of patients in whom a clinical diagnosis of bacterial endocarditis is made, positive blood cultures cannot be obtained, even when a variety of media are inoculated and incubated both aerobically and anaerobically.^{6, 8, 58} This situation is particularly apt to occur in patients who have had recent antibiotic therapy. In such circumstances, treatment should be begun with penicillin G, streptomycin and probenecid, according to the schedule outlined for enterococcal endocarditis. If the response to this form of therapy is unsatisfactory, the following steps are in order: the dose of penicillin should be doubled, after which

other antibiotics may be added, preferably singly and on a trial basis. Clues as to the possible etiology should not be overlooked. For example, if endocardial infection occurs following a wound infection, abscess or pneumonia, or after cardiac surgery, the possibility of a resistant staphylococcus should be considered and a therapeutic trial with methicillin, vancomycin or kanamycin instituted. When there has been preceding genitourinary tract manipulation or infection, there is greater likelihood of gram-negative bacillary endocarditis, and chloramphenicol, colistin or kanamycin should be given.

INFREQUENT CAUSES OF ENDOCARDITIS

Infections caused by organisms such as group A streptococci, group B streptococci, non-beta hemolytic group M-reacting streptococci,⁶⁴ the meningococci and gonococci can be treated effectively with aqueous procaine penicillin in a dose of 1.2 million units intramuscularly given every 6 hours for 3 to 4 weeks. Probenecid is also advised. In endocarditis due to pneumococci, therapy during the first 5 days should be modified by administering intravenous aqueous crystalline penicillin in large doses.¹¹

Endocarditis due to *Pasteurella*-like organisms was effectively treated with large doses of penicillin G plus streptomycin or one of the broad-spectrum antibiotics for 3 to 4 weeks.⁷⁷

We have successfully treated a patient with *Vibrio fetus* endocarditis, using tetracycline in a dose of 0.5 gm. orally every 6 hours for 4 weeks, and streptomycin, 0.5 gm. intramuscularly every 12 hours, for 2 weeks.

Bacteroides infections have responded to tetracycline plus streptomycin or high doses of penicillin G therapy for 6 weeks.^{17, 23, 63} It is difficult to recommend a therapeutic program for brucella endocarditis with confidence in view of the fact that all 8 patients in 2 recent series expired.¹³ It seems reasonable to employ a combination of tetracycline plus streptomycin in maximal doses for at least 6 weeks.¹³

A variety of fungal agents, including species of coccidioides, cryptococcus, blastomyces, histoplasma, candida, aspergillus and mucor have been implicated uncommonly in endocarditis.^{52, 79} These higher organisms undoubtedly account for an occasional case in which the clinical diagnosis is not substantiated by positive blood cultures. Of increasing importance are those cases caused by candida species following courses of broad-spectrum antibiotics, steroids or antimetabolites. Similarly, cardiac surgery and the prolonged use of polyethylene intravenous catheters may also be associated with candida endocarditis.² Cases of candida endocarditis have proved almost universally fatal, despite amphotericin B therapy; in the only reported successful case, surgical removal of the valvular vegetations was apparently responsible for the outcome.⁴⁰ The occurrence of the "higher bacteria," including nocardia and actinomycetes, as causes of endocarditis has been reviewed.^{5, 39} In some instances, penicillin has been effective in eradicating the organisms.

ENDOCARDITIS FOLLOWING CARDIOVASCULAR SURGERY

Although infrequent, endocarditis following cardiovascular surgery carries a mortality rate of about 50 per cent.^{14, 15, 47} Staphylococci are involved in 80 per cent of these cases, 50 per cent being *S. albus* strains.⁴⁷ In addition, pseudomonas and other gram-negative rods are being reported with increasing frequency.

A number of cases of endocarditis has been observed following intro-

duction of prosthetic cardiac valves. Similarly, ventriculo-atrial shunt procedures performed for the relief of hydrocephalus have been identified with a significant incidence of endocardial infection^{3, 27, 42, 47, 68, 73}. In the majority of these cases, antibiotic therapy has been ineffective until the "infected" prosthesis has been removed from the circulatory system. Further, the removal procedure should be carried out promptly, before the clinical condition of the patient deteriorates to the point where operation becomes impossible.

Treatment of Penicillin-Allergic Patients

That severe and even fatal reactions may result from penicillin administration to hypersensitive patients has been amply demonstrated. This fact, examined in the light of the unique efficacy of this drug in potentially lethal endocarditis, in a sense confronts the clinician with the Scylla and Charybdis of antibiotic therapy. It is generally agreed, however, that when patients, known to be penicillin-sensitive, are afflicted with endocarditis which can be expected to respond to this antibiotic, its administration should be attempted, utilizing stringent precautions.^{1, 25, 35, 78, 80} It is mandatory that antihistamines, steroids, pressor agents and equipment for maintaining an airway be at hand. Initially, 1 unit of aqueous crystalline penicillin should be added to a 500 ml. bottle of 5 per cent dextrose in water being administered intravenously. After 20 minutes, if an untoward reaction has not occurred, 10 units of penicillin should be added to the same bottle. This procedure is repeated at 20 minute intervals, adding tenfold increments of penicillin until therapeutic levels are achieved. If a moderate reaction appears, administration of antihistamines or steroids should be begun. Up to 100 mg. of prednisone by mouth, or 300 mg. of hydrocortisone hemisuccinate by vein, may be required daily. Polyethylene intravenous catheters are to be avoided, particularly when steroids are being administered, because of the danger of superimposed candida endocarditis.⁷⁵ Alternatively, in penicillin-allergic patients with enterococcal endocarditis, ristocetin therapy may be used.

In the penicillin-sensitive patient with endocarditis due to staphylococci resistant to penicillin G, the question of cross-hypersensitivity to methicillin arises. This problem has not as yet been resolved, although cases have been reported in which methicillin administration has been tolerated by patients in whom a previous allergic reaction to penicillin G has occurred.^{48, 67} In such patients, however, it is probably safer to start methicillin administration by the desensitization procedure outlined above, beginning with a 1 mcg. dose. Alternatively, if methicillin therapy does not prove feasible in these patients, vancomycin should be employed.

PROPHYLAXIS

In an earlier section, the frequent occurrence of transient bacteremia was noted, and its enhancement after dental extraction, instrumentation of the genitourinary tract and obstetrical and gynecologic procedures

was emphasized. In some series of patients with bacterial endocarditis, historical data strongly suggest a direct relationship between prior dental extraction and the genesis of endocarditis.^{50, 84} Although, as has been pointed out by Finland,²⁰ there is no incontrovertible evidence supporting the concept that prophylaxis is beneficial, most physicians especially interested in bacterial endocarditis advise the use of antibiotic prophylaxis in susceptible patients undergoing dental procedures or other manipulations known to be associated with an increase in transient bacteremia. Until it is demonstrated conclusively that prophylaxis is not valuable, it is our view that it should be given.

Studies with several antibiotics have indicated that prophylaxis, though it results in a decrease in bacteremia, does not prevent it.³³ Thus, whatever efficacy there is in prophylaxis presumably derives from the prompt eradication of organisms which have become implanted on a diseased valve or other abnormal cardiac structure. For this reason, it is strongly recommended that the agent given for purposes of prophylaxis be continued for at least three days after the procedure has been carried out. Where a focus of bacteremia persists, as at the site of an operative procedure, prolongation of the period of antimicrobial therapy is in order.

In the case of dental extractions, bacteremia is more frequent and more intense after multiple extractions;²⁸ for this reason single extractions are probably preferable. When infection of the gums is prominent, pre-extraction treatment with penicillin can be expected to lessen the intensity of bacteremia at the time of operation.

The use of antibiotics in the prevention of bacterial endocarditis has recently been reviewed in detail by Hook and Kaye.³³ They concur that prophylaxis with an appropriate antibiotic, in patients susceptible to bacterial endocarditis, is indicated. The following regimens are suggested as guidelines: for procedures (especially dental extractions) on the upper respiratory tract, in which penicillin-sensitive nonhemolytic streptococci are most apt to enter the blood stream, 600,000 units of procaine penicillin G should be given at least one hour prior to the procedure and repeated on the following three days. In patients who are sensitive to penicillin, 0.25 gm. of erythromycin every six hours orally may be substituted; the drug should be begun two hours before the procedure, and continued for three days.

In the case of genitourinary tract instrumentation and delivery, in which case enterococci or gram-negative rods are the most frequent infecting agents, 1.2 million units of procaine penicillin G plus 1 gm. of streptomycin should be administered one hour before the procedure and repeated every 12 hours for three days. Alternatively, tetracycline, 0.5 gm. every six hours, may be given for three days. This same program may be applied in the case of intestinal tract manipulations. Finally, because of the increasing prevalence and devastating consequences of penicillin G-resistant staphylococcal infections after cardiac surgery, 4 to 8 gm. of methicillin should be administered parenterally for at least three days, beginning just prior to the operation.

SUMMARY

In the past century, understanding of the etiology and pathology of bacterial endocarditis has progressed impressively. Until the advent of potent antimicrobial agents, effective treatment of the disease was lacking and the prognosis was essentially hopeless. The introduction of the sulfonamides marked the beginning of a new era in respect to the outlook in bacterial endocarditis, and the use of penicillin resulted in a high rate of cure in nonhemolytic streptococcal endocarditis. The emergence of penicillin-resistant staphylococci, and the increased incidence of endocardial infection due to gram-negative organisms and fungi, by-products of the antibiotic era and of the spectacular advances in cardiac surgery, have created new and often extremely difficult therapeutic problems.

Prompt diagnosis, based on recovery of the causative organisms in blood cultures, coupled with utilization of special laboratory techniques for determination of drug sensitivity patterns and of serum antibiotic levels, should permit effective treatment in a majority of patients.

The various antibiotic regimens, generally shown to be effective against the organisms most often implicated in infectious endocarditis, have been reviewed. Prophylaxis of bacterial endocarditis associated with dental extractions and other operative procedures has also been discussed.

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Current Considerations Regarding the Prevention of Primary and Recurrent Rheumatic Fever

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MODERN antistreptococcal therapeutics have been primarily directed toward the prevention of primary and recurrent rheumatic fever because of the serious nature of this sequel of streptococcal infection. During the past 15 years a wealth of evidence has been accumulated that treatment of streptococcal infections sufficient to eradicate this organism will prevent rheumatic fever.^{9, 43, 53} Furthermore, the high risk of recurrence of rheumatic fever in persons who are infected with group A streptococci subsequent to their primary rheumatic attacks has resulted in the vigorous promotion of programs of continuous chemoprophylaxis against streptococcal infection in rheumatic subjects.^{11, 49} A number of controlled studies attest the value of these programs in preventing recurrent rheumatic fever and concomitantly rheumatic heart disease.^{40, 47} Thus, the recognition and adequate therapy of streptococcal infection and continuous antistreptococcal prophylaxis in rheumatic subjects provide means by which the problem of rheumatic heart disease may be attacked directly.

The mortality from and severity of rheumatic fever have been declining for several decades. A continuation or even acceleration of these

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favorable trends has occurred during the time that antistreptococcal therapy and prophylaxis have been available.^{1, 3, 28, 44} Rheumatic subjects have been observed through long periods of freedom from recurrent attacks and it has been suggested that continuous prophylaxis in all rheumatic subjects, especially those without evidence of heart disease, may not be necessary.¹⁷ Streptococcal disease has been observed frequently among school-age children,^{12, 21, 25, 27, 36} but rheumatic fever rarely occurred in these populations. In view of the infrequency of the rheumatic sequel, the necessity of effective antibiotic therapy of all bacteriologically identified streptococcal infections has been questioned.^{15, 23}

The purpose of the first part of this discussion is to show that, despite favorable trends, appreciable numbers of cases of rheumatic fever still occur. These indicate that a sizable reservoir of undetected or inadequately treated streptococcal infections is present. Therefore, at this time, emphasis should be placed on the accurate detection and effective treatment of these infections. In the second part, suggested modifications of current procedures for antistreptococcal therapy and prophylaxis will be examined. Evidence will be presented that these modifications are based on features of the natural history of streptococcal infections and rheumatic fever that are presently being studied and additional data must be obtained before changes in current therapeutic and prophylactic regimens may be accurately designed.

EPIDEMIOLOGY OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Precise data on the incidence of rheumatic fever in specific areas of the United States as a whole are not available because it has only recently become a generally reported disease. Intensive surveys of small populations indicate that many cases are not reported. Data on mortality from rheumatic heart disease and the incidence of rheumatic heart disease are somewhat easier to obtain, and it is likely that an examination of these statistics which demonstrate a marked decrease in mortality and a more modest decrease in the incidence of rheumatic heart disease have been responsible for the general impression that rheumatic fever is a disappearing disease. The impressive decline in mortality from rheumatic fever in the most susceptible age group in the United States since 1920 is illustrated in Table 1. An even sharper decline is evident in mortality from heart disease. Although congenital cardiac disease is included in this category, heart disease consists mainly of rheumatic heart disease in this age group.

Approximately 3 per cent of men examined for military service in World War I had evidence of heart disease, mainly rheumatic; in World War II inductees, a prevalence of rheumatic heart disease of 1.6 to 1.8 per cent was reported.^{28, 55} Surveys conducted by different observers on children of elementary school age in various parts of the United States during the past two decades have not shown a significant change in the prevalence of rheumatic heart disease, as illustrated in Table 2. The summarized studies were conducted by performing intensive cardiac examinations of all members of randomly selected samples of representative populations rather than by examining children referred to a cardiac study center from many sources without standard criteria. The latter method results in lower rates which in several surveys over the same period of

**Table 1. Mortality Rates for Rheumatic Fever
and Heart Disease in Children Age 5-14
in the United States***

YEAR	DEATHS PER 100,000	
	Rheumatic Fever	Heart Diseases
1920	4.4	17.4
1930	3.0	12.1
1940	2.6	8.0
1950	1.8	2.1
1959	0.5	0.8

* Modified from Stamler.⁴⁴

time as those presented in Table 2 did not reveal a significant change in the prevalence of rheumatic heart disease.⁵⁴

Evidence that the severity of rheumatic fever has decreased over the past 30 to 40 years has been collected in several studies.^{1, 3, 28, 44} The study by Bland and Jones³ of 4 groups of 100 patients each, observed during the first year of the 4 decades since 1920 in Boston, demonstrated a decrease in the incidence of valvular disease from 75 to 60 per cent and a decrease in marked cardiac enlargement from 30 to 14 per cent.

Most observers agree that there has been a decrease in the incidence of primary and recurrent rheumatic fever over the same period of time but no accurate methods have been found to measure this decrease retrospectively. A recent report⁴¹ of an intensive study of the incidence of rheumatic fever in Minnesota provides excellent evidence that current attack rates of rheumatic fever are of much greater magnitude than is appreciated. Between 1950 and 1954 Minnesota physicians reported an average of 187 cases of rheumatic fever

Table 2. Prevalence of Rheumatic Heart Disease

YEAR	LOCATION	AGE GROUP	NUMBER EXAMINED	RHEUMATIC HEART DISEASE RATE PER 1000	REMARKS
1939-41	Eureka, Calif.	5-18	2450	20	Northern Calif. (ref. 42)
"	Susanville, Calif.	5-18	732	11	Ref. 42
"	Redland, Calif.	5-14	2633	3.8	Southern Calif. (ref. 42)
1944-45	Denver, Colorado	12-19	1845	16.3	Girls only (ref. 54)
"	Dublin, Georgia	11-14	401	10	Ref. 33
1946-47	Rural Connecticut	11-15	1092	16	Ref. 31
"	Hartford				
"	Bridgeport	Conn.	11-15	1732	21.3
"	Waterbury				Large cities (ref. 31)
1947-48	Ansonia				
"	Derby	Conn.	7th and 8th grades	754	60
"	Shelton				Crowded population in poor housing (ref. 32)
? 1950	Colorado	6th grade	11,157	6.7	Rural and city schools (ref. 14)
1950	Madison, Wisc.	7th grade	893	28	Ref. 34
1957-58	Nashville, Tenn.	11-14	4039	25	Ref. 35

yearly to the Department of Health. A questionnaire survey to which 50 per cent of the physicians in the state responded revealed that in 1955 these physicians diagnosed and treated 2397 cases of acute rheumatic fever. A 13 per cent sample of these cases was studied in detail and 72 per cent of the diagnoses were found to satisfy the Jones criteria. Thus, 1650 acceptable cases of rheumatic fever were diagnosed. In 65 per cent of validated cases, carditis was detected clinically. A comparable sample of 16 per cent of the physicians who had not responded to the questionnaire was interviewed according to the same techniques employed in the sample studied in detail. From this sample it was estimated that another 1000 cases of rheumatic fever had been treated by physicians that had not responded to the questionnaire. Thus, a total of approximately 2600 cases of rheumatic fever were seen by physicians in Minnesota (population 3.19 million) during this year. About 85 per cent of these were initial attacks. This is in striking contrast to the average of 187 cases reported during the preceding 5 years and probably represents a much more accurate indication of the true incidence of rheumatic fever in this state. An extrapolation from these figures indicates that more than 100,000 persons had experienced untreated or inadequately treated streptococcal infections during this time. Another report from the heart disease control group in Chicago reveals that over 500 cases of rheumatic fever occur yearly in this city of which more than 300 are primary attacks.⁴⁴

Sizable local outbreaks of rheumatic fever are not passé. In a community of about 10,000 inhabitants in North Dakota during an interval of approximately 11 weeks in the spring of 1961, 18 cases of rheumatic fever were diagnosed;⁵⁷ 11 cases occurred in children attending the first 11 school grades. Although the streptococcal disease rate could not be determined, a retrospective survey of a sample of school children demonstrated that 40 per cent harbored group A streptococci of which 80 per cent were typable (types 5 and 12 were prevalent). Antistreptolysin determinations on sera from these school children showed that about 50 per cent had titers greater than 200, indicating that they had probably recently experienced streptococcal infection. Many of the children had received inadequate antibiotic therapy of 3 to 5 days' duration for their streptococcal infections, including some of those who developed rheumatic fever.

These epidemiological data are presented to demonstrate that despite favorable trends in the mortality and severity of acute rheumatic fever and rheumatic heart disease, their incidence has not been accurately determined and may be considerably larger than is appreciated. The control of acute rheumatic fever and its cardiac sequelae is still a major problem, necessitating improved case finding and effective therapy rather than a complacent attitude insecurely based on present progress.

PREVENTION OF RHEUMATIC FEVER

Soon after the introduction of penicillin and the demonstration that treatment of streptococcal infections for ten days would eradicate streptococci from the oropharynx, the important observation was made that this therapy prevented the subsequent development of acute rheumatic fever. The extensive controlled studies of Rammelkamp and associates⁸ at the Streptococcal Disease Laboratory clearly demonstrated that penicillin therapy that eliminated the streptococcus prevented rheumatic fever in more than 98 per cent of patients. Other

studies⁴⁷ begun during World War II in groups of patients who had experienced an initial rheumatic attack demonstrated that chemoprophylaxis adequate to prevent acquisition of streptococci would prevent recurrences of rheumatic fever. Continuation of these studies during the past 10 to 15 years at centers for the care of children with rheumatic fever have shown the remarkable effectiveness of penicillin and sulfonamides in keeping these children free from recurrent rheumatic disease.^{18, 26} These effective measures have been widely publicized by the American Heart Association and other professional organizations to foster the prevention of initial^{7, 29} and repeated attacks of rheumatic fever throughout the United States. The 1960 recommendations¹¹ are summarized in the following schedule:

- A. Treatment of streptococcal infections.
 1. Benzathine penicillin.
One injection of 900,000 to 1,200,000 units in adolescents and adults.
One injection of 600,000 to 900,000 units in children.
 2. Procaine penicillin with 2 per cent aluminum monostearate in oil.
One injection of 600,000 units every 3 days for 3 doses in adults.
One injection of 300,000 units every 3 days for 3 doses in children.
 3. Oral penicillin.
200,000 or 250,000 unit tablets 3 times daily for 10 days in children, and adults.
- B. Prevention of streptococcal infection.
 1. Benzathine penicillin.
One injection of 1,200,000 units each month.
 2. Oral sulfonamide such as sulfadiazine or sulfisoxazole.
0.5 gm. a day in children under 60 pounds every day.
1.0 gm. a day in older children and adults every day.
 3. Oral penicillin.
200,000 units twice daily continuously.

In spite of the efficacy of the measures for antistreptococcal therapy and prophylaxis and the wide dissemination of this information, primary and recurrent rheumatic fever and rheumatic heart disease continue to occur as illustrated in the first section of this discussion. What are the reasons for their persistence?

Factors Responsible for the Continuing Occurrence of Rheumatic Fever

A group A streptococcal infection always initiates a rheumatic attack. Failure to recognize this antecedent infection or inadequate therapy of the infection is responsible for failures in preventing rheumatic fever. Retrospective analyses of the records of hundreds of rheumatic patients have produced unequivocal evidence of these facts.^{18, 20, 56}

There is at present no good economical substitute for the bacteriological culture method for the recognition of hemolytic group A streptococci, and the ease with which this technique may be practiced or the service obtained by all physicians makes its general use *obligatory*.

AN OFFICE CULTURE METHOD FOR IDENTIFYING GROUP A STREPTOCOCCI. Many physicians have set up modest office bacteriological laboratories to identify streptococcal illnesses in their practice. They have obtained a small incubator, sterile swabs and commercially prepared, disposable blood agar plates which are available at a total cost per patient of about 65 cents from many medical supply houses. After refreshing their memory with several visits to a good diagnostic bacteriology laboratory, they are able to inoculate and interpret their own culture plates. In taking cultures, to obtain best results, the swab should be firmly rubbed over both tonsillar areas and the posterior pharyngeal wall. A blood agar plate should be inoculated within one hour by rubbing the swab with a rolling motion over a small area of the agar surface. For house calls, several plates in the physician's bag make this a simple procedure. Before incubation, material from the inoculated area of the plate should be spread on the surface of the agar with a bacteriological loop to obtain isolated colonies. Stabbing into the agar with the loop provides adequate subsurface growth necessary to detect some hemolytic streptococci that produce better hemolysis under reduced oxygen tension. Plates containing 5 per cent sheep blood provide the best results. These plates may be stored in the refrigerator in plastic bags for 3 or 4 weeks without deterioration. Group A streptococci produce clear-zone hemolysis, easily differentiated from the greenish, incomplete hemolysis that characterizes *viridans* streptococci on sheep blood agar.

A physician finding group A streptococci in the throat or nasopharynx of a patient with a sore throat or other upper respiratory infection should prescribe chemotherapy that will eradicate these organisms.

RISK FACTORS. Evidence to support the above general statement may be obtained by considering the risk of developing rheumatic fever in relation to the stages or manifestations of streptococcal parasitism as outlined below.

1. *Sore Throat or Respiratory Illness with Streptococcal Parasitism:* RISK OF RHEUMATIC FEVER 0. The patient in this category represents a problem in recognition for the physician. The presence of group A streptococci on culture concurrent with symptoms indicates that he may have a streptococcal infection, and only a series of at least two determinations of a streptococcal antibody (antistreptolysin O, anti-hyaluronidase, antistreptokinase, etc.) at intervals of a minimum of 10 days showing no rise in titer can identify a patient in this category accurately.⁴⁸ This is rarely practicable. Therefore, because of the risk that he may have a streptococcal infection, it is recommended that this patient receive one of the designated courses of antistreptococcal therapy.

2. *Asymptomatic Streptococcal Parasitism:* RISK OF RHEUMATIC FEVER 0. Implantation of streptococci usually on the mucous membrane of the nasopharynx is the initial event after exposure to these organisms. A culture demonstrating group A streptococci is evidence of this event. If the exposure is minimal or some degree of antistreptococcal immunity is present, this is a transient stage^{39, 52} but a person parasitized in this manner may be able to transmit streptococci to others more susceptible. If he is found by bacteriological culture and not precisely identified by absent antibody increase, he should be given antistreptococcal therapy. The only benefit would be his removal as a potential transmitter of streptococci.

3. Streptococcal Infection Without Overt Illness: RISK OF RHEUMATIC FEVER 1. This patient is almost never recognized. Only intensive surveillance of patients who have had a primary attack of rheumatic fever have made it possible to identify such persons by multiple cultures and routine serial antibody determinations.⁴⁸ A rise in antibody titer represents the only evidence of streptococcal infection in these subjects. They develop recurrences of rheumatic fever⁴⁸ and probably comprise most of the patients in whom rheumatic fever appears without an overt related respiratory illness.^{20, 56} If by good fortune this patient is identified by antibody determinations after a culture survey or as a result of a clinically recognizable streptococcal illness in a sibling or other close contact, he should have antistreptococcal therapy. Even though treatment may be late, there is evidence that delayed therapy will still reduce the risk of subsequent rheumatic fever.⁹

4. Streptococcal Infection with Nonexudative Sore Throat or Respiratory Illness: RISK OF RHEUMATIC FEVER 1. Clinically this patient cannot be distinguished from the patients in category one. He can only be identified by a positive culture and by demonstrating a rise in streptococcal antibody in serial determinations.⁴⁸ Although the risk that this patient will develop rheumatic fever cannot be estimated at this time, it is definite and the serious nature of this sequel and the inability to predict the likelihood of subsequent rheumatic heart disease provide a firm basis for recommending antistreptococcal therapy.

5. Exudative Streptococcal Pharyngitis: RISK OF RHEUMATIC FEVER 2. This is the classic form of streptococcal infection. In addition to the pharyngeal exudate, these patients often have dysphagia, fever, cervical adenitis and leukocytosis. The finding of group A hemolytic streptococci in the throats of patients with exudative pharyngitis or tonsillitis provides the most easily obtained evidence of a streptococcal illness. Studies of military populations experiencing epidemic and nonepidemic streptococcal infections using these features as major criteria for diagnosis have consistently demonstrated that approximately 3 per cent of untreated patients in this group will develop acute rheumatic fever.³⁷ Almost all of these patients demonstrate a rise in serum streptococcal antibody titer and many are persistent oropharyngeal streptococcal carriers.³⁷

Studies in civilian populations have not generally used exudative streptococcal pharyngitis as a criterion of a streptococcal illness so that comparison of rates of rheumatic fever among civilians cannot be made. However, in a study of Chicago children with pharyngitis,⁴³ the rheumatic fever rate based on the presence of streptococcal exudative pharyngitis, antibody increase and persistent streptococcal carriage was 2.5 per cent. Since only two cases of rheumatic fever occurred in these children, this rate is not of high statistical significance. It is quite possible that the streptococcal illnesses described in this category represent either more intensive streptococcal exposure or more intensive host response, which may provide a greater stimulus for rheumatic inflammation. Patients with exudative pharyngitis of virus etiology who are transient group A streptococcal carriers may be confused with patients in this

category. The absence of a streptococcal antibody rise will identify them.

6. *Exudative Streptococcal Pharyngitis with Intensive Antibody Response: RISK OF RHEUMATIC FEVER* 3. Stetson⁴⁵ studied the immune response measured as the increase in titer of streptolysin O antibody in more than 1900 young airmen after exudative streptococcal pharyngitis. His analysis indicated that a small increase in antistreptolysin O titer was associated with a low attack rate for rheumatic fever, and that the attack rate increased proportionately in groups of patients showing progressively higher antibody responses. The group showing an increase in antistreptolysin O titer of more than 250 units had an attack rate of 5.5 per cent.

These variations summarize the natural history of streptococcal infections and indicate the variability in the occurrence of rheumatic fever in different forms of streptococcal parasitism. The numerical values of risk have no precise relationship but are only estimates based on incomplete data. The study of Chicago children with sore throats reported by Siegel, Johnson and Stollerman⁴³ illustrates the variation in the rheumatic fever attack rate according to the form of streptococcal parasitism or infection. Data taken from this investigation are summarized in Table 3 to show this variation and the association of these figures with some of the categories of risk that have been discussed. Asymptomatic streptococcal illnesses (category 3) were not included in this study but there is good evidence that rheumatic fever may be initiated by an unrecognized streptococcal infection. Several investigators^{13, 20, 56} report that from 23 to 40 per cent of patients seen in recent years after primary rheumatic fever did not have an evident antecedent pharyngitis.

From consideration of these characteristics of streptococcal parasitism and disease, it is apparent that the problem of identification of streptococcal illness carrying any risk of rheumatic fever is not easy. This is especially true in young children who commonly have atypical or mild streptococcal illnesses.³⁰ An important tool, streptococcal antibody determination, is generally not available to physicians as a diagnostic aid and under ideal circumstances a streptococcal antibody increase may

Table 3. Variations in Attack Rate of Rheumatic Fever*

STREPTOCOCCAL CRITERIA	NUMBER OF PATIENTS	RHEUMATIC FEVER ATTACK RATE (%)	CATEGORY
1. Pharyngitis with positive throat culture for group A streptococci	519	0.4	1 and 4
2. Pharyngitis, positive culture and ASO titer rise	228	0.9	4
3. Exudative pharyngitis and positive culture	186	1.0	5 and 1
4. Exudative pharyngitis, positive culture, ASO titer rise and persistent streptococcal carriage	81	2.5	5

* Data modified from Siegel et al.⁴³

not be found in time for diagnosis and effective therapy before the onset of the rheumatic attack. Because of the difficulty in recognizing streptococcal infections by clinical examination, physicians must make use of methods for culturing group A hemolytic streptococci to increase diagnostic accuracy. Patients with respiratory infection or sore throat must be "sold" on the need to consult a physician. If they have positive cultures, they should receive proper antistreptococcal therapy even though in some instances these conservative criteria for treatment will include some persons who are carriers with superimposed nonstreptococcal illnesses. Techniques are not available to detect silent streptococcal infections which may initiate rheumatic fever so that present efforts to reduce the prevalence of rheumatic fever must be concentrated on detection and effective treatment of recognized and bacteriologically confirmed streptococcal infections.

Prevention of Recurrent Rheumatic Fever

Today approximately 98 per cent of patients survive their initial attack of rheumatic fever.²⁴ Seventy to 75 per cent of these patients suffer no permanent detectable cardiac injury;^{19, 51} nevertheless, the threat to life and cardiac function does not end when the rheumatic attack is over.^{2, 4, 51} Instead of acquiring some degree of immunity to future attacks, the rheumatic subject is more susceptible than originally. Long-term, intensive studies of patients who have had rheumatic fever have provided data describing the natural history of recurrent rheumatic fever. Because these details are important in formulating the most efficient program for preventing recurrent rheumatic fever and permanent heart disease, they will be briefly reviewed.

Cumulative rheumatic fever recurrence rates vary considerably in different reports depending on the criteria employed to define recurrences and on the duration of observation. Before the use of chemoprophylaxis, recurrence rates averaged greater than 50 per cent in two groups observed for ten years.^{2, 4} A comparable rate in the Cooperative Study patients on prophylaxis observed for five years was 14 per cent.⁵¹ It was found in another investigation that rheumatic recurrences occurred as frequently as 24 per cent of instances after "break-through" streptococcal infections in patients on oral penicillin prophylaxis.⁴⁶ These figures indicate that the management of repetitive attacks is a continuing problem.

It has been demonstrated, when complete clinical, bacteriological and serological tests are performed, that recurrent rheumatic fever can be initiated only by group A streptococcal infection. The type of infection may vary from subclinical to classic exudative pharyngitis; indeed, many recurrences follow clinically undetectable infections.^{22, 26} The risk of repeated attacks is greater during the first three years after the initial attack and then continues at a lower rate for many years.⁴⁷ Repetitive attacks in patients with *heart disease* usually produce more cardiac damage and recurrences in patients with marked valvulitis, cardiac enlargement or congestive failure carry a poor prognosis.^{16, 51} It is evident that these features of recurrent rheumatic fever make it imperative that all opportunity for streptococcal infection be avoided by con-

tinuous prophylaxis. In contrast, *patients without primary cardiac involvement* are much less likely to develop subsequent heart disease.^{6, 19} If it can be firmly predicted that patients without carditis during their initial rheumatic illness will remain free of carditis if recurrences occur, it is probable that these persons will require only limited prophylaxis. Data describing the subsequent cardiac history of patients who have had different forms of primary rheumatic attacks have been collected for many years. These data will be examined to find out if the diverse patterns of rheumatic fever have a constancy of prognosis that will permit modifications of prophylactic measures without undue risk of rheumatic heart disease.

Long-term studies^{2, 4} conducted before streptococcal prophylaxis was possible, as exemplified by the reports of Ash and Bland and Jones, revealed that patients who had experienced rheumatic fever could be divided into four groups: those who developed carditis during their primary attack, demonstrated cardiac involvement after recovery and had rheumatic heart disease at follow-up examination; those with carditis and cardiac damage whose heart disease had later regressed; those who did not have carditis during the primary attack and did not develop heart disease thereafter; and those free of carditis in the initial stage who subsequently developed heart disease (designated emergent heart disease in Table 4). The natural history of rheumatic heart disease, which is in essence the distribution of patients in these groups, is illustrated in Table 4. In this table the studies of Ash and Bland and Jones conducted in the pre-prophylaxis area are compared with the Cooperative Rheumatic Fever Study and with the investigation of Feinstein et al. of patients maintained on chemoprophylaxis after their initial rheumatic attack. Although these studies conducted at different times are not precisely comparable, they do illustrate differences of a degree that are probably significant.

Table 4. Natural History of Rheumatic Heart Disease

	AUTHORS			
	Ash ²	Bland and Jones ⁴	Cooperative Study ⁵¹	Feinstein et al. ¹⁹
Total patients.....	537	1000	324	370
Years of observation.....	10	10	5	7.2*
Prophylaxis after first attack.....	—	—	+	+
Per cent of total patients with:				
Carditis at onset.....	59	65	68	51
Heart disease at follow-up.....	53	58	28	24
Regression of heart disease.....	6	7	40	27
No carditis at onset.....	41	35	32	49
No heart disease at follow-up.....	31	27	29	49
Emergent heart disease.....	10	8	3	0

Average.

All of these observers state that recurrent attacks of rheumatic fever in patients with rheumatic heart disease maintain or cause further cardiac damage. Precise figures to illustrate this point are not presented by Ash and Bland or in the Cooperative Study. Feinstein and Spagnuolo¹⁷ reported that 70 per cent of patients with prior carditis had clinical evidence of additional cardiac involvement during a recurrent attack. Taranta⁵⁰ observed that patients with heart disease are more likely to develop recurrences after a streptococcal infection and stated that this risk is directly proportional to the degree of existing heart disease and to the number of previous rheumatic attacks.

As indicated in Table 4, most of the patients observed during the pre-prophylaxis period who developed carditis during their primary rheumatic attack had heart disease at the follow-up examination, whereas half of the patients on continuous prophylaxis who had carditis initially were free of heart disease at follow-up. The probability of regression of heart disease was 5 to 6 times greater in the patients on prophylaxis. It is likely that the prevention of recurrences by continuous prophylaxis against streptococcal infections was a major factor responsible for the significantly lower prevalence of heart disease in patients given preventive medication. The high risk of recurrence and the probability of increased cardiac involvement with repeated rheumatic attacks provide unqualified justification for continuous antistreptococcal prophylaxis of unlimited duration in these patients.

Another recorded feature of the natural history of rheumatic heart disease is the development of cardiac involvement after the primary rheumatic attack in patients with no evidence of carditis initially (emergent heart disease in Table 4). This is not a frequent finding^{2, 4, 51} and some observers have reported that heart disease does not appear in subsequent years in patients free of cardiac involvement during primary rheumatic fever.^{6, 17}

Feinstein and colleagues,¹⁹ after observing 370 patients on continuous prophylaxis for an average of 7.2 years, have reported on the constancy of the clinical characteristics of rheumatic fever in this group. Approximately one-half of these patients did not have carditis with their primary attack and none of these patients demonstrated carditis with recurrences (column 4, Table 4). In a later report,¹⁶ 27 patients without previous carditis were described who had recurrent attacks; only two of these patients had carditis (pericarditis only), and they recovered without evident residual heart disease.

In the Cooperative Study Group which received continuous prophylaxis after primary rheumatic fever, a few rheumatic recurrences occurred but were not associated with emergent heart disease (column 3, Table 4). In contrast, Bland and Jones and Ash report that 8 to 10 per cent of patients developed heart disease (emergent heart disease) even though they did not have carditis during their primary rheumatic illness (columns 1 and 2, Table 4). Ash² reported that 82 per cent of cases of emergent heart disease appeared during rheumatic recurrences. Bland and Jones⁵ also stated that the "delayed appearance of heart disease was clearly associated with co-existing signs of rheumatic fever in two thirds of the group" with emergent heart disease. Rammelkamp⁵⁸ described 11 young military recruits with a childhood history of rheumatic fever or chorea. These men were observed daily during an attack of rheumatic fever and did not have heart murmurs. Subsequently, three developed valvular heart disease, one during an observed rheumatic recurrence.

A possible explanation for the discrepancy between the findings of Feinstein and the other observers is that the group of patients that did not develop emergent heart disease received continuous antistreptococcal prophylaxis which greatly decreased the intensity and frequency of streptococcal parasitism or infection for them. An example of the intensity of this challenge in the absence of prophylaxis was presented by Coburn and Moore in 1940.¹⁰ They compared the incidence of streptococcal infections and rheumatic recurrences in a group of 17 rheumatic children during three successive years. In 1937 while they were receiving continuous sulfonamide prophylaxis no infections and no recurrences occurred. In 1938 and 1939 without prophylaxis there were 15 identified streptococcal infections and 11 rheumatic attacks in this group.

It is likely that the very low rate of emergent heart disease in the Cooperative Study Group and the complete freedom from heart disease in all of the patients initially free of carditis followed by Feinstein is a new and artificial feature of the natural history of rheumatic fever resulting from continuous antistreptococcal prophylaxis. Therefore, it would be misleading to propose limited or interrupted prophylaxis for patients in this category after they had been selected by this technique.

After recovery from rheumatic fever without carditis, patients should receive continuous prophylaxis until the opportunity for acquisition of group A streptococci in their environment is minimal. This means through childhood, adolescence and parenthood. The "find and treat" approach for controlling streptococcal infection is too hazardous, especially in socio-economic groups of high streptococcal prevalence, to be a satisfactory substitute for prophylaxis.

Studies have clearly demonstrated that continuous parenteral benzathine penicillin given at monthly intervals is the best method of prophylaxis.^{46, 49} Sulfonamides and oral penicillin, even when they are taken faithfully, are not as effective as injected depot penicillin.⁴⁶ Sulfadiazine in controlled studies appears to be slightly more effective than oral penicillin.⁴⁶

Preventive antistreptococcal medication is expensive and sometimes a medical or psychological hazard. Yet, the ubiquity of group A streptococci and the failure of patients to seek medical care because of the subtlety of streptococcal infections make continuous prophylaxis the only no-risk method for the prevention of recurrent rheumatic fever at this time.

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Therapy of Acute Bacterial Gastroenteritis

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BACTERIAL GASTROENTERITIS remains a significant cause of death in countries with underdeveloped public health and sanitation facilities. In the United States, and in other countries with reasonably adequate public health standards, death resulting from bacterial gastroenteritis is infrequent.³³ The morbidity produced by bacterial diarrheas is unknown since patients with diarrhea may not seek medical attention or, if they do, may be treated without benefit of stool culture. The memory for short-lived episodes of diarrhea is faulty. Retrospective surveys demonstrated an incidence of diarrhea of 5 to 10 per cent per year whereas on careful prospective study, especially in rural areas, the incidence increased to 20 to 60 per cent per year.⁷² The percentage of attacks of diarrhea which have a bacterial origin ranges from less than 1 per cent in urban to 30 per cent in rural areas. In 1961, 12,500 cases of shigellosis, representing a probable reservoir of 125,000 cases and carriers, were recorded. These findings emphasize the frequency with which bacterial diarrhea may be encountered.

The role of antibiotics in decreasing mortality due to bacterial gastroenteritis is relatively minimal. In 1950-1955 the death rate due to bacterial gastroenteritis in the United States was 2 per 100,000 population. These figures contrast sharply with the 400 deaths per 100,000 population recorded in 1870, a rate still prevalent in underdeveloped countries.³³ Most of the improvement in mortality resulted from improved sanitation and public health facilities and the use of parenteral fluid therapy. By 1935, before the use of antibiotic agents, the death rate in this country

had dropped to 10 per 100,000 population. Thus, the overall importance of adequate sanitation and public health facilities in the prevention of bacterial gastroenteritis must be recognized.

PATHOGENESIS OF BACTERIAL DIARRHEA

The exact mechanism whereby bacteria produce bowel infection is unknown. Variation in virulence of organisms plays a role in the establishment of infection. For example, feeding experiments in man demonstrated that for *Salmonella pullorum* one billion organisms were required to induce disease; *Salmonella newport*, however, produced diarrhea when only 200,000 organisms were fed.^{50, 51} Similarity between bacterial and host antigen may be a factor in determining virulence. An antigenic relationship between *Salmonella typhimurium* and the host caused increased virulence in animal experiments.³³ Antibiotic therapy alters the normal flora of the gut and predisposes to establishment of infection.^{19, 26, 28} Decreased gastric acidity, especially following gastrectomy, allows more organisms to pass into the small intestine. The establishment of a bacterial flora in the normally sterile small bowel does not, in itself, cause diarrhea.^{12, 23} Thus, patients with hepatic cirrhosis have increases in their small intestinal bacterial contents without consequent diarrhea.⁴⁵ Multiplication of pathogenic organisms in the small intestine is needed for the production of diarrhea. That bacterial diarrhea is a disease primarily of the small intestine is demonstrated further by the failure of pathogens placed in the colon either to multiply or to produce diarrhea.²³ Pathologic studies confirm that colonic involvement is a late event in the course of the disease. Stasis of bowel contents experimentally produced by mechanical obstruction, opium administration or anticholinergic agents favors establishment of disease when bacterial pathogens are introduced.²⁷ Such experiments correlate well with findings that bacterial disease occurs more often in areas of relative stasis such as terminal ileum and above obstructing lesions.^{5, 36} These observations support the doubts expressed concerning the use of stasis-producing drugs in bacterial diarrhea.²²

Detailed information concerning mechanisms of production of diarrhea in bacterial gastroenteritis is lacking. Normally, large quantities of fluid pass into the gut lumen and are reabsorbed.⁷³ The numerous bacteria and bacterial and tissue metabolic products may be a significant osmotic load producing increased transfer of fluid into the lumen and decreased flux back from the lumen. Inflammation may increase fluid exudation and functional mucosal disruption from bacterial invasion may affect absorptive mechanisms. In the most severe forms of diarrhea, daily fluid losses may approach the amount of fluid which normally enters the gut. Losses as high as 50 per cent of total body water are recorded. Usually, however, losses are much smaller and the ability to reabsorb fluid even during gastroenteritis continues.

Derangements of motility may contribute to the diarrhea. Certainly rapid transit time allows less insorption. Whether rapid transit occurs because of an irritative effect on motor function or whether it is a normal response to continued distention produced by increased luminal fluid volume is unknown. In chronic nonbacterial diarrheas colonic manometric studies have demonstrated that contractions are greater in amplitude but less in frequency. Segmenting waves, which normally slow passage of contents, may be absent and liquid stool is forced into the rectum without the usual decrease in water content. Thus, in chronic diarrheal states the large intestine shows a basic pattern of atony. These observations may explain the failure of anticholinergics since these agents inhibit contractions and thus increase decompensation. Fluid passes through the atonic colon readily, causing continued rectal stimulation. Recum-

bency decreases the urge to defecate by keeping the rectum free of gravity drainage.¹¹ Similar motility studies in acute bacterial diarrhea are unavailable.

RECOGNITION OF BACTERIAL DIARRHEA

The only accurate means of differentiating bacterial from viral diarrhea is by bacteriologic examination of the stool.⁷² Viral diarrhea usually is accompanied by mild constitutional signs, loose watery stools not containing blood or mucus, and a self-limited course of three to five days' duration. In bacterial diarrhea the constitutional response may be more severe, the stools mucoid or bloody, and the course prolonged or marked by complications, but most often bacterial and viral diarrheas are clinically indistinguishable. Stool culture should be performed in every instance of diarrhea to increase diagnostic accuracy. In certain situations such study is even more obviously indicated. These include family, institutional or community outbreaks, diarrhea persisting over 48 to 72 hours, bloody or mucoid stools, a clinical course of increased severity with a fecal-fluid loss of 1000 cc. or more per day, diarrhea in a postoperative patient or in one being treated with antibiotics, diarrhea in patients with gastrectomies, etc.⁵⁹ Although many such selective criteria exist, the failure to study stools in the absence of these criteria results in missed diagnoses.

A Gram stain of mucus or debris-containing fluid portion of stool is an aid in diagnosis when leukocytes are present or specific organisms are found. Leukocytes usually indicate the diarrhea is of bacterial origin. In staphylococcal enterocolitis large numbers of gram-positive cocci in grape-like clusters may be seen. The finding of gram-negative, comma-shaped, slender rods indicates that cholera is present. Stool smear thus strengthens the suspicion that diarrhea is bacterial in origin and may be diagnostic in the instances referred to above, but in all cases stool culture should be performed. Stools sampled within 2 hours of passage offer the best chance of demonstrating bacterial pathogens.⁶⁴ Even under ideal circumstances, however, only 85 per cent of cultures will demonstrate the causative pathogens.⁴¹ Samples should include any cellular debris or mucus shreds. If the sample cannot be placed in culture media within 2 hours, 1 gram of fresh material should be emulsified in 10 cc. of 30 per cent glycerol saline solution (Table 1).⁶⁴ In this solution organisms are stable for 5 to 7 days at 20° C. Pathogenic organisms will not survive if multiplication of nonpathogenic, rapid acid-producing bacteria occurs. The solution then turns from pink to yellow indicating that the specimen is unsuitable for identification of patho-

Table 1. Sach's Solution⁶⁴

Glycerol.....	30 cc.
Sodium chloride.....	0.42 gm.
Dipotassium phosphate (anhydrous).....	0.31 gm.
Monopotassium phosphate (anhydrous).....	0.1 gm.
Distilled water.....	70 cc.

Add phenol-red solution to give a pink color. Sterilize at 120° C for 15 minutes; pH should be 8. If color changes from pink to yellow, the solution should be discarded.

genic bacteria. Specimens may be mailed if they are placed in a well padded, waterproof container* and marked as a bacteriologic specimen. Pathogens usually are nonlactose fermenters, but this criterion is not absolutely reliable. The differentiation of pathogenic organisms by ordinary bacteriologic methods is sometimes difficult and tests for complete identification take two to five days.¹ It may be necessary to begin therapy before the organism is identified. Antibiotic treatment should not be started until specimens for culture have been obtained.

MAJOR NONBACTERIAL COMPLICATIONS

Certain life-threatening complications of gastroenteritis are not directly related to the specific bacterial agent involved and are not treated by chemotherapeutic drugs. These complications include dehydration, shock, renal insufficiency and endotoxin shock.

DEHYDRATION. Daily losses of up to 17 liters of fluid may produce prostration within hours in choleraform illnesses. Studies in epidemic cholera, the archetype of severe, dehydrating bacterial enteritis, illustrate the problems involved.^{41, 73} Table 2 shows fluid and electrolyte losses in cholera. Stool electrolyte concentration varies directly with volume, but fluid usually is lost in excess of salt. Since dehydration may cause death within hours, rapid, quantitative evaluation of the degree of dehydration is required for proper therapy. Decreased skin turgor, decreased eye globe tension, absence of sweating, and extreme thirst are clinical manifestations of dehydration. Elevations in the hematocrit and in serum sodium and protein concentrations are used to evaluate dehydration (Table 3). These values are deceptive, however, if sodium has been lost in large amounts, if the patient is bleeding or is anemic, and in malnourished individuals. The clinical status may deteriorate so rapidly in fatal dehydration that changes in these blood values may not be appreciated. Whole blood specific gravity (normal = 1.057) correlates best with clinical developments. Graded copper sulfate solutions for determining blood specific gravity are easy to make, remain stable indefinitely, and provide an accurate and rapid means of assessing severe dehydration.⁵⁸ The method follows.

Determination of Specific Gravity of Whole Blood by the CuSO₄ Method

1. Venous blood is collected without stasis into heparin at a ratio of 0.2 mg. heparin per cc. of whole blood.

Table 2. Stool Composition in Cholera⁴¹

CLINICAL SEVERITY VOLUME/24 HRS. Na (mEq./L.) K (mEq./L.) HCO ₃ ⁻ (mEq./L.)				
> 3 liters daily	7000 cc.	104	20	34
< 3 liters daily	992 cc.	79	26	15

Adapted from Tables 4 and 5, reference cited.

* Mailing cases may be obtained from the Arthur H. Thomas Company, Philadelphia.

**Table 3. Cholera: Blood Values During Therapy in Severe Group
(> 3 Liters Stool Daily)⁷³**

CLINICAL STATUS	HEMATOCRIT (%)	WHOLE BLOOD SPECIFIC GRAVITY	CO ₂ (mEq./L.)	WHOLE BLOOD OSMOLARITY (mOsm/L.)
Admission.....	54.4	1.067	18.1	361
Rehydration.....	47.6	1.054	18.5	346
At 24 hours.....	34.4	1.049	23.0	346
Convalescence.....	36.2	1.050	28.0	315
Normal.....	40-44	1.056-1.058	25-30	300-320

Adapted from Table 2, reference cited.

2. A series of standard copper sulfate solutions is made:
 - (a) Four pounds of CuSO₄·5HOH is placed in a 4 liter volumetric flask.
 - (b) 2.5 liters of distilled water are added.
 - (c) Solution is agitated for 5 minutes at 20° C.
 - (d) Solution is decanted and filtered through glass wool.
 - (e) 488 cc. of this solution diluted to 1 liter gives a solution with specific gravity 1.100.
 - (f) A volume of the 1.100 solution is measured into a 100 cc. volumetric flask, less by 1 ml. than the value of the second and third decimal points of the specific gravity desired, viz., for a 1.055 solution 54 cc. would be diluted to 100 cc.
 - (g) A series of dilutions at 0.002 intervals should be made from 1.035 to 1.075.
3. Drop of whole blood is dropped from a 1 cm. height by medicine dropper.
4. Drop is observed during the 10 seconds following loss of momentum.
 - (a) If drop rises, its specific gravity is less than test solution.
 - (b) If drop falls, its specific gravity is greater than test solution.
 - (c) If drop remains motionless, its specific gravity is the same as the test solution.

Motion of the blood drop after 10 seconds following loss of momentum has no significance, as the specific gravity changes with formation of copper proteinate at the interface.

SHOCK. The major cause of shock in gastroenteritis is severe dehydration. In a cholera epidemic 30 per cent of the patients were in shock when first seen.⁴¹ Correction of dehydration obviated the need for pressor agents, blood transfusion, dextran, plasma or serum albumin. Blood loss ordinarily is not a factor. Occasionally, however, mucosal necrosis is severe enough to cause bleeding.

ACUTE RENAL INSUFFICIENCY. Dehydration and shock may produce acute tubular necrosis. This complication developed in 11 per cent of patients hospitalized with cholera. Prerenal causes of acute renal insufficiency such as dehydration and shock, and obstruction to urine flow should be excluded before the diagnosis of acute tubular necrosis can be established. In early tubular injury neither oliguria nor a fixed urine specific gravity may be found. However, oliguria with low urine urea and elevated urine sodium concentrations are the usual manifestations of acute tubular injury.⁵⁶

ENDOTOXIN SHOCK. Shock persisting after rehydration and correction of severe blood loss requires immediate clinical re-evaluation.

Cardiogenic shock must be considered. Bacteremic or endotoxin shock is thought of when other, more usual, causes have been eliminated.^{32, 34, 44} Endotoxin is believed to be a phospholipid-polysaccharide-protein complex. Shock not explained by other causes occurs in 10 to 30 per cent of patients with gram-negative septicemia and is blamed on endotoxin release.⁷ Thirty to 60 per cent of patients with gram-negative septicemia in shock die. In man, endotoxin shock begins with a chill followed within three hours by hypotension and fever. Restlessness, hyperventilation and apprehension occur. As hypotension develops, the patient has either a cold, cyanotic and mottled skin with a thready pulse or a warm, dry and flushed skin with a palpable pulse—so-called “warm shock.” Diarrhea, vomiting, sweating and oliguria appear within 12 hours. The survival rate is better in patients with warm shock. A transient initial rise in total peripheral vascular resistance occurs during developing shock followed by a fall.³⁰ Vascular resistance probably is altered by constriction of venules and dilatation of precapillary arterioles. These changes are accompanied by decreased cardiac output. Elevated norepinephrine levels may play a role in the disordered activity of the vascular bed. Blood volume, at least in man, appears to be unchanged. Acute tubular injury due to shock or bilateral renal cortical necrosis, possibly on an immunologic basis, occurs. Renal cortical necrosis was produced experimentally as part of the Shwartzman phenomenon. Whether a similar response causes cortical necrosis in man is unknown.

TREATMENT

Therapy of the Major Nonbacterial Complications

DEHYDRATION AND SHOCK. Degrees of fluid loss similar to those seen in cholera may occur in bacterial diarrhea in this country. Patients with persistent fluid loss in excess of 1000 cc. daily need hospitalization. Parenteral therapy will be needed to correct dehydration and prevent collapse. Patients with pre-existing disease such as diabetes mellitus, congestive heart failure, renal disease, etc. should be hospitalized sooner since they present special problems in management. Initially, rapid intravenous infusions of saline are used. In severe cases infusions at rates of up to 80 cc. per minute may be needed. The presence of other illnesses such as cardiac or renal disease requires modification of the rapidity with which rehydration is accomplished. Rapid rehydration is continued until dehydration is corrected. Subsequent replacement is based on clinical fluid balance measurements. After initial rehydration to restore extracellular fluid volume, fluids similar to those administered in diabetic acidosis may be utilized. Suggested solutions have an approximate composition of 100 mEq. per liter of sodium and 100 mEq. per liter of either chloride or bicarbonate. The osmotic deficit is made up with dextrose. Intravenous potassium replacement is needed if losses are continuous and feedings cannot be tolerated. In continuing disease urine and stool output and imperceptible losses estimated as 0.3 cc./kg. per hour should be replaced. Fluids are increased 10 per cent for each degree of fever over 99° F. Treatment for acidosis in dehydrating enteritis may

be necessary (Table 3). If blood pH values are below 7.35 or bicarbonate levels below 15 mEq. per liter, intravenous sodium bicarbonate may be administered. Each 0.46 to 0.80 mEq. per kilogram of body weight raises serum bicarbonate levels 1 mEq. per liter. Replacement should be over a 24 hour period. More than 5 mEq./kg. per day is rarely needed.

Since shock in gastroenteritis is commonly due to fluid loss, correction of the dehydration usually is sufficient treatment. Plasma losses in peritonitis may be corrected with 5 per cent albumin solution (Albumisol). Continuing blood loss should be replaced by whole blood despite the risks of hepatitis, transfusion reactions and septicemia.⁴⁹ Blood loss of less than 500 cc. ordinarily requires no replacement in adults.⁷⁵ Dextran probably is contraindicated since it blocks the reticulo-endothelial system, promotes experimental Shwartzman phenomena, and further dehydrates tissues.

ACUTE TUBULAR NECROSIS. Management of acute tubular injury consists primarily of limiting fluid and electrolyte intake.⁵⁶ The measured perceptible losses and the estimated imperceptible losses are replaced continuously by intravenous fluids. One hundred grams of glucose added to the daily intravenous solutions decreases protein and fat catabolism and minimizes the release of potassium, metabolic acids and urea. Infusion sites should be rotated to prevent sepsis. A weight loss of 500 grams (1 pound) per day is desirable. The uremic syndrome, metabolic acidosis and potassium intoxication, when life threatening, may be managed with peritoneal dialysis or hemodialysis. Fifteen to 25 per cent of deaths occur following onset of diuresis which usually begins in three to 14 days. Mortality in the diuretic phase has been attributed to excessive loss of fluid and electrolytes. Although polyuria may be due, in part, to accumulation of fluid and electrolytes resulting from catabolism, salt depletion continues to be a danger and electrolytes must be replaced. Renal concentrating power usually returns to normal within two to 12 months.

ENDOTOXIN SHOCK. In endotoxin shock pressor agents should be started promptly to maintain systolic blood pressure at 80 mm. Hg.^{7, 32, 34, 39, 40} Agents of choice are Metaraminol (Aramine) and Mephen-termine (Wyamine).⁵⁵ Either agent is used at concentrations of 0.1 to 1.0 mg. per cc. to minimize volume loading. Pressor agents improve survival rates of patients in shock with gram-negative septicemia by 20 per cent. Blood pressure should not be maintained with pressor agents before correcting fluid losses since dehydration is the major cause of shock in gastroenteritis. Angiotensin II (Hypertensin) which acts on precapillary arterioles may be a more effective agent in endotoxin shock. It is given at a rate of 3 to 10 micrograms per minute.^{17, 57} Blocking agents have no demonstrated value.

Although the physiologic rationale for the administration of steroids in endotoxin shock is uncertain, clinical evidence supports their use in severe toxemic states and hypotension associated with gram-negative septicemias.^{7, 40, 54} In endotoxin shock hydrocortisone levels are elevated but responsiveness to ACTH administration persists. Patients who ultimately died showed a greater response to ACTH than did survivors.

Hydrocortisone disappearance rates were accelerated in survivors as compared to those dying in shock. Thus, disturbances in steroid metabolism may be involved in the pathogenesis of endotoxin shock. When other causes of shock have been eliminated, parenteral hydrocortisone, 500 mg. every eight hours, may be added to the therapy outlined above. Steroids are given for one to three days. Dosage is decreased slowly as toxemia decreases and blood pressure becomes stable.

Symptomatic Treatment of Mild Disease

Most cases of bacterial diarrhea are mild and self-limited and are managed with home care. Frequent feedings of small quantities of salt and glucose-containing fluids such as commercial soft drinks maintain fluid balance adequately. Vomiting and diarrhea are improved by a short (24 to 36 hour) period of starvation which may be used if fluid losses are not significant. As illness subsides, feedings are increased in consistency. If diarrhea or vomiting recur, diet should be simplified again. Cramping pain can be controlled by antispasmodics such as atropine sulfate U.S.P. 0.4 mg. by mouth t.i.d. or diphenoxylate hydrochloride with atropine sulfate (Lomotil, 5 mg. t.i.d.), but the potential dangers of gut atony and stasis should be considered. Antispasmodics are useful in controlling distressing symptoms but do not substitute for proper management of fluid loss.

Chemotherapy of Sepsis and Fulminant Disease

In seriously ill patients in whom bacteremia complicating bacterial gastroenteritis seems likely, a stool smear should be studied and stool and blood cultures obtained. In cholera, no antibiotic therapy is indicated,⁴¹ and in staphylococcal diarrhea penicillin and methicillin are the agents of choice (Table 4). If no diagnostic clue exists to indicate the choice of antibiotic therapy and appropriate cultures have been started, the empiric use of parenteral chloramphenicol and kanamycin is warranted (Table 4).^{40, 53} There is no need to start antibiotics immediately in most patients with symptoms limited to gastroenteritis. In these patients fluid loss and dehydration are the life-threatening complications. In some patients with continuing diarrhea in whom adequate fluid replacement is difficult to maintain, an antibiotic may be life-saving. Chloramphenicol and kanamycin are continued until specific disc antibiotic sensitivities are known. Since proper selection of antibiotics significantly lowers mortality, antibiotic therapy should then be altered, especially if the clinical situation has not improved greatly.^{7, 32, 40, 47, 48} Chloramphenicol should be used cautiously in infants and in patients with liver or renal disease^{10, 15, 56, 69}. Bone marrow depression due to chloramphenicol can be anticipated by performing serial reticulocyte counts, serum iron determinations⁶³ and bone marrow examinations. Reticulocyte levels below 0.5 per cent and serum iron concentration increasing during drug therapy indicate bone marrow depression. Initial antibiotic therapy can be followed by an abrupt elevation in temperature eight to 12 hours later with an accompanying drop in blood pressure. Kanamycin toxicity ordinarily is not significant

Table 4. Parenteral Chemotherapy in Septicemia Associated with Bacterial Gastroenteritis^{31, 32}

CONDITION*	DRUGS OF CHOICE*†	ALTERNATE CHOICES*†
Etiologic agent unknown ^{40, 47, 48, 53}	Chloramphenicol and kanamycin	Tetracycline and streptomycin
Shigella ⁸	Tetracycline ²⁴	Sulfisoxazole; chloramphenicol
Salmonella ^{52, 67}	Chloramphenicol ⁵⁶	Penicillin G ⁶⁰
Escherichia.....	Tetracycline and streptomycin	Colistin; chloramphenicol and kanamycin
Staphylococci.....	Penicillin G and methicillin	Vancomycin; chloramphenicol
Proteus.....	Tetracycline and streptomycin	Kanamycin and penicillin G
Pseudomonas ¹³	Polymyxin B	Colistin; tetracycline
Clostridia ⁷⁰	Penicillin G	Tetracycline

* References cited refer to specific drug action in disease or to specific drug toxicity.

† Maximal recommended doses in gm./day for 70 kg. patient are listed. Dosage generally should be administered in equally divided amounts during a 24 hour period (intramuscular = IM; intravenous = IV); chloramphenicol 3.5 (IM or IV), kanamycin 1.5 (IM), tetracycline 0.6 (IM), streptomycin 2.0 (IM), penicillin G 6.0 (IM or IV), methicillin 8.0 (IM or IV), polymyxin B 0.20 (IM), colistin 0.35 (IM), vancomycin 2.0 (IV), and sulfisoxazole 12.0 (IM or IV).

in short-term therapy in patients with normal renal function. However, ototoxicity develops rapidly in patients with renal insufficiency. The gastrointestinal tract should be allowed to drain freely and anticholinergic or narcotic agents used only to control cramps. Although Kaopectate may have some inactivating effect on endotoxin, it too produces dehydration and stasis and probably is contraindicated.

SPECIFIC ENTERITIDES

In the following sections, certain problems related to specific etiologic agents are discussed. Table 4 contains recommendations concerning selection of parenteral antibiotics to be used in bacteremia associated with gastroenteritis and in fulminating gastroenteritis. Table 5 contains

Table 5. Oral Antibiotic Therapy in Enteritis

CONDITION*	DRUG OF CHOICE* †	ALTERNATE CHOICES* †
Shigellosis ⁴⁶	Sulfisoxazole	Tetracycline; chloramphenicol
Salmonellosis ⁶⁷	Chloramphenicol	
Escherichia.....	Neomycin and polymyxin B	

* References cited refer to specific drug action in disease or to specific drug toxicity.

† Maximal recommended dose in gm./day for 70 kg. patient. Dosage generally should be administered in equally divided amounts during a 24 hour period; chloramphenicol 3.5, tetracycline 2.0, sulfisoxazole 12.0, neomycin 4.0, and polymyxin B 1.4.

similar recommendations concerning selection of oral antibiotics to be used in the majority of patients with bacterial gastroenteritis. These recommendations are based on studies reported in the literature. Optimal treatment depends on selection of the best antibiotic based on sensitivity tests of the organisms causing disease in the individual patient.^{33, 46, 47, 48}

Shigella

Shigellosis is one of the two common causes of bacterial enteritis in this country and is fatal in 1 per cent of cases. Shigella are transmitted by a feces-hand-mouth route.⁷² Failure of hand washing following fecal contamination is the major factor responsible for spread of the disease.^{68, 72} Animal reservoirs play no role in shigellosis. Shigellosis has an acute onset following an incubation period of 1 to 6 days. The diarrhea usually is described as mucoid, purulent or bloody, but most patients actually have watery diarrhea.⁷² Abdominal cramping, vomiting, fever and chills may precede the diarrhea. High fever and chills cannot be attributed to endotoxin alone since bacteremia can occur. Smear of the stool reveals many leukocytes. Sigmoidoscopy may show sharply defined ulcers with a mucopurulent base; material from these ulcers yields a high number of positive cultures and positive smears for leukocytes.

Eighty to 90 per cent of cases of shigellosis resolve without antibiotic treatment. The carrier state may persist, however, for as long as five years and is ended by antibiotic therapy. Antibiotic therapy is mandatory as an epidemiologic precaution. Household contacts of the index case should be cultured and treated.⁷² In institutional outbreaks treatment of clinical cases alone will not affect the course of the epidemic. A 10 per cent incidence of illness in a closed social group is indication for prophylactic therapy with sulfisoxazole (Gantrisin) 1 gram b.i.d. for seven days.²⁵ Complications are limited to mild arthritis of larger joints two to three weeks following the episode. Reports of ulcerative colitis and regional enteritis following a shigellosis epidemic in 1935 have never been confirmed.²² Vaccination has been attempted but results are inconclusive.

Salmonella

Salmonellosis, the other common cause of gastroenteritis in the United States, has increased in incidence and in significance as a public health problem.⁶⁶ The increase is in *Salmonella* species other than typhosa and is a real change rather than a difference in reporting.^{43, 66} The four syndromes in salmonellosis were recognized by Osler: gastroenteritis, typhoidal syndrome with septicemia, focal manifestations, and the carrier state. In one large series gastroenteritis, most commonly caused by *S. typhimurium*, occurred in 68 per cent; the typhoidal syndrome in 9 per cent, with *S. choleraesuis* the usual etiologic agent; and focal manifestations, most frequently due to *S. choleraesuis*, in 7 per cent. Sixteen per cent of patients with salmonellosis are asymptomatic carriers. *Salmonella typhimurium* is the organism most often carried. A history of gastroenteritis is obtained in only 50 per cent of carriers. An overall mortality of 4.1 per cent has been recorded.⁶⁶ *S. choleraesuis* and *S. typhimurium* accounted for most of the deaths.

The manifestations of *Salmonella* enteritis range from asymptomatic infection to a choleric form illness.²⁹ Nausea, abdominal cramps, anorexia and vomiting are common. Weight loss, fever and chills occur but usually are transient. The

diarrhea varies from loose normally-colored stools through "pea-soup stools" to watery-mucoid stools. Frank intestinal bleeding, especially in children, may be seen. A secondary illness, either typhoidal in type or focal, or both, may develop days to weeks after recovery from enteritis. *Salmonella schottmüller* and *S. choleraesuis* are the agents most commonly producing delayed secondary illness.⁶⁶

Therapy for *Salmonella* enteritis is supportive. Antibiotics do not shorten the clinical course, decrease relapse rate or decrease the incidence of complications in cases of enteritis.^{46, 52} Antibiotics increase the rate at which stools are cleared of pathogens but do not decrease the incidence of carriers. In the extraintestinal syndromes treatment with chloramphenicol decreases mortality.^{46, 67} Prevention depends on control of animal reservoirs and chronic human carriers.⁷¹ In some surveys *Salmonella* carrier rates rose from 5 per cent to 30 per cent as animals moved from the farm to stockyards. Contamination of meat increased to 51 per cent of the specimens following slaughter and dressing.³

Treatment of the human carrier presents continued problems. The chronic carrier is the patient who continues to excrete organisms one year after clinical recovery from the initial episode. The carrier rate is at least 2 per 100,000. Gallbladder disease occurs in more than 50 per cent of the carriers and decreases the likelihood of cure with antibiotics alone. In carriers without gallbladder disease intensive and prolonged therapy with antibiotics should be tried, but frequently is disappointing. In carriers with gallbladder disease, antibiotic therapy without cholecystectomy is almost uniformly unsuccessful. Cholecystectomy in the chronic carrier is warranted mainly as a public health measure.⁷¹

The use of phenolized typhoid-paratyphoid A and B vaccine (Typhoid and Paratyphoid Vaccine) is effective in decreasing morbidity for *Salmonella* enteritis. The vaccine is administered intramuscularly in 0.3 cc., 0.5 cc. and 0.7 cc. amounts in adults at seven to 14 day intervals.⁷⁶ Each cubic centimeter contains 1,000,000,000 killed *Salmonella typhosa* and 250,000,000 killed paratyphoid A and B organisms each. A 0.5 cc. booster is necessary yearly in endemic areas and every three years in the United States.²⁰ *Salmonella choleraesuis*, which most commonly causes serious disease in this country, is not included in commercially available vaccine.⁴²

A complication results from the recent finding that organisms with mixed rates of lactose fermentation can reproduce the clinical picture of salmonellosis. These organisms, the Arizona group, are obviously important. Bacteriologic differentiation of pathogens depends partly on different rates of lactose fermentation. Pathogens characteristically ferment lactose slowly or not at all. Slow lactose-fermenting forms of the Arizona group may be discarded as a "paracolon." This group may be considered in any enteritis which appears to be bacterial in origin but lacks the usual bacteriologic criteria.

Escherichia

Escherichia coli were considered to be saphrophytes in the gut for many years. Following serologic separation, certain strains were shown to cause epidemic

diarrhea. Epidemics in newborn nurseries and rarely in urban populations are described. The significance of isolation of pathogenic strains in sporadic cases is uncertain because of the high incidence of carriers. The disease is acute in onset and has an incubation period of 1 to 12 days. Fever, vomiting, intermittent diarrhea and, at times, a choleric form syndrome with dehydration occur. Infants under two years are affected most frequently but scattered adult cases occur in family contacts. Studies indicate that drug resistance is developing and that sensitivity studies are of importance in drug selection.

The group of organisms presently classified with the *Escherichia*, the alkali-genes *dispar* group, is a rare cause of disease ranging from mild enteritis to a severe typhoidal syndrome.¹⁸ These organisms can be found on blood culture and serologic responses following clinical disease have been demonstrated.^{62, 74}

Cholera

Cholera is an endemic and potentially pandemic disease usually transmitted by water through fecal contamination. There is a short incubation period of one-half to 3 days. The diarrhea may range from a very mild state to overwhelming fluid loss. An unusual form occurs in which paralytic ileus produces a fluid-filled gut without obvious diarrhea. As in all other enteritides, the very young and the aged have the poorest prognosis.

A 60 per cent mortality in untreated severe cases may be reduced to 30 per cent with parenteral fluid therapy.^{41, 73} Improvement can be followed by observing stool color changes from white rice-water stools to pea-soup stools to normally colored stools. Stools are strongly alkaline and a pH of 7.0 or greater is maintained for one hour at room temperature. Evaluation of the role of antibiotic therapy is difficult since organisms disappear spontaneously by the first or second day of illness. There is no evidence that improvement follows the use of presently available antibiotics.

Prevention of cholera depends upon effective quarantine of cases and careful hygiene. Stools should be discarded directly from the patient into large containers containing strong disinfectant (1 per cent creosol). General sanitation measures to prevent contamination of water are most important. Prior vaccination reduces mortality in epidemics by 16 per cent to 24 per cent. The vaccine contains 8,000,000,000 organisms/cc. of the Inaba and Ogawa strains in phenol (Cholera Vaccine). An initial deep subcutaneous injection of 0.5 cc. is followed in seven days by 1 cc. with a 1 cc. booster every six months.

Staphylococcus

Antibiotic therapy may lead to the selective growth of antibiotic-resistant organisms, especially *Staphylococcus aureus*.^{4, 28} The presence of staphylococcus in the stool does not necessarily mean that disease exists.³⁵ When present in predominating numbers, various clinical syndromes can result: mild or severe diarrhea without demonstrable enteric lesions or enteritis with pseudomembrane formation. Pseudomembranous enterocolitis may appear in the absence of staphylococcal organisms.¹⁶ These syndromes are found most frequently in postoperative patients being treated with broad-spectrum antibiotic "prophylaxis." Mild gastrointestinal complaints occurring 3 to 5 days after operation may be replaced by a sudden choleric form illness with nausea, vomiting, fever and diarrhea leading to oliguria, shock and death. Large volumes of fluid may remain loculated in the gut and not appear as diarrhea.

Fluid and electrolytes should be replaced, previous antibiotic therapy discontinued, and prompt treatment with penicillin and methicillin begun (Table 4).⁶¹ Reestablishment of normal intestinal flora by administration of yogurt and saline extracts of fresh, noninfective stools has been advocated.¹⁴ Yogurt and stool extracts may be given by tube intraduodenally or by enema in 60 cc. doses. *Lactobacillus acidophilus* and *bulgarius* (*Lactinex*) 4 tablets q.i.d. is used for the same purpose. In a nasal carrier of coagulase-positive *Staphylococcus aureus* topical bacitracin-neomycin ointment reduces carrier rate and postoperative infections. Prophylactic parenteral therapy is not helpful and may be dangerous.^{2, 26, 65} *Proteus* and *Pseudomonas* may produce enteritis under circumstances similar to those predisposing to staphylococcal enteritis.⁵³

Clostridia

Although the clostridia ordinarily are not considered as causing enteritis, they are normal inhabitants of the bowel and may produce disease in debilitated individuals.^{26, 37} Clostridial enteritis may present as a mild diarrhea with slight fever. In patients with leukemia or lymphoma under chemotherapy, fulminating disease with fever, tachycardia and development of hemolytic anemia may occur.⁶ Anemia is followed by hemoglobinuria, jaundice, anuria and death. Lymphomatous invasion of the gut and malnutrition are the most common underlying factors. Clostridia invades damaged tissue and surgical removal of diseased segments, when feasible, may be needed for effective treatment.

Parenteral antibiotic therapy (Table 4) should be started following culture. Polyclonal antitoxin containing *Clostridium perfrigens* and *Cl. novyi* antitoxin 27,000 units each together with *Clostridium septicum* antitoxin 13,500 units is given intravenously every four hours. Blood should be replaced as needed. Oxygen given under increased atmospheric pressure by means of compression tanks may depress growth of the organism and enhance clinical recovery.⁹

SUMMARY

Advances in public health and sanitation, the use of parenteral fluids, and antibiotic therapy have decreased deaths due to bacterial gastroenteritis in this country to a rate of 1-2/100,000 in 1961. Mortality remains high in underdeveloped countries, due mainly to the lack of adequate public health facilities. Failure to obtain stool cultures in cases of acute diarrhea results in an underestimation of morbidity due to bacterial diarrhea. Viral diarrhea is frequently the clinical diagnosis in acute, short-lived gastroenteritis, but there is no reliable method of differentiating bacterial from viral gastroenteritis without bacteriologic examination.

Fluid loss and its consequences are the greatest threats in most patients with gastroenteritis and proper replacement is the most important initial therapeutic procedure. In patients with septicemia and fulminating diarrhea due to bacterial gastroenteritis, the empiric use of chloromycetin and kanamycin is justified until the results of antibiotic sensitivity tests are available. Antibiotic therapy is most successful when based on such

tests. In many instances of mild gastroenteritis, antibiotic treatment should be withheld until bacteriologic studies are completed since chemotherapy often is more important from an epidemiologic standpoint than it is for the patient.

In addition to Shigella, Salmonella and cholera groups, the classic causes of bacterial gastroenteritis, Escherichia strains and incompletely classified forms like the Arizona group may produce gastroenteritis. Underlying disease, especially of the gut, and antibiotics given for other purposes enhance the likelihood that diarrhea is due to organisms such as Clostridia, Staphylococcus and Pseudomonas which ordinarily do not cause gastroenteritis.

Therapy in bacterial gastroenteritis generally is satisfactory when based on an appreciation of underlying and epidemiologic factors, the need for fluid replacement, and the proper choice of antibiotics dependent on bacteriologic study.

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Selected Aspects of Urinary Tract Infection

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URINARY TRACT INFECTION* is an important general medical problem. It comprises a group of common episodic infectious illnesses and, in addition, appears to play an insidious, causal role in the natural history of a number of noninfectious conditions. These include prematurity and neonatal death among offspring of women with bacteriuria during pregnancy, chronic renal failure and hypertension.^{19, 22}

The purpose of the present review is to summarize selected aspects of urinary tract infection concerned with its epidemiology, recognition and treatment.

FREQUENCY OF OCCURRENCE

Certain general principles are useful in measuring the importance or impact of a disease. These include an estimate of mortality—the number of individuals who die as a result of it. Another important measure is that of morbidity—the number of persons who sicken or are disabled by it. There are several aspects of mortality data which are frequently overlooked. First, there is the problem of clinical recognition of urinary tract infection as a cause of death. Most authors cite statistics to indicate that

* The term "urinary tract infection" is used rather than a series of components, such as, cystitis, urethritis, pyelonephritis, etc., since it is virtually impossible in many instances to distinguish precisely which parts of the tract are or are not involved.

the condition is frequently overlooked and emphasize that pyelonephritis is the most frequent cause of renal failure.²⁰ Careful autopsy examination may not, however, clarify the nature of the renal lesion since considerable controversy still exists regarding acceptable anatomic criteria of pyelonephritis.²¹ Hayman's¹¹ introduction to a discussion of chronic pyelonephritis illustrates this aspect of the problem of precise anatomic diagnosis:

"Chronic pyelonephritis is a fashionable diagnosis at the present time. Physicians are fairly used to fashions in therapeutics, and perhaps even in the importance of some laboratory procedures, but are less accustomed to think of fashions in pathological diagnoses. Yet in one university clinic almost all renal lesions in the autopsy population up to about 1925 were called chronic glomerulonephritis. Then when the ideas of Volhard and Fahr penetrated beyond the Alleghanies, this diagnosis was no longer made. All chronic kidney disease was designated arteriolonephrosclerosis until about 1940 when, as the result of the papers of Weiss and Parker, chronic pyelonephritis became the most common pathological diagnosis."

Data derived from autopsy populations are essential to our knowledge concerning natural history but conclusions concerning prevalence or incidence of urinary tract infection based on postmortem examinations are hazardous. This is due to the highly selected nature of population samples under study. In the excellent study of the demographic features of those persons who were autopsied in 1955 in the United States, McMahan²² found that there were marked variations in the likelihood with which postmortem examinations were performed, depending upon a number of important variables. These included race, sex, geographic location and economic status. Thus, the extent to which these variations may introduce bias must be taken into account in applying frequency data based on autopsies to other population groups. The fact that pyelonephritis was found in 5 or 10 or 20 per cent of autopsies performed in a given hospital over a period of years provides very little help to the practicing physician in estimating how often he can expect to encounter the disease. Further, it is difficult to generalize about the incidence of urinary tract infection based upon the experience of a hospital or clinic population owing to the fact that, while the number of affected individuals observed per unit time may be known, the size of the group at risk or community from which they were drawn is rarely identified.

One of the most useful studies on the frequency of urinary tract infection is that of Fry et al.,⁸ based on carefully recorded systematic observations in a general practice setting in England. Since the population of the practice was known, the authors were able to conclude that "the rate of occurrence of acute urinary infections each year was almost 12 per 1000 of the practice. The family doctor with an average size list (of 2500) can therefore expect to treat about 30 patients each year. In the country as a whole there may be as many as 500,000 cases each year. About 4 times as many females were affected as males. There was a very definite peak in young women (20-30 age group) and a constant high level thereafter. In males, attacks were more common after the age of 40—possibly because of bladder neck obstruction." They inves-

tigated the subsequent course of 125 patients 4 to 6 years later and concluded that these infections did not lead to chronic pyelonephritis during the interval studied.

Loudon and Greenhalgh²⁵ performed a similar kind of study in which they surveyed a sample of patients in another English general practice and calculated patient consulting rates for urinary tract infection. They found, as did Fry and his co-workers, "that a general practitioner can expect to see about 12 cases of urinary infection a year for every 1000 patients on his list." The ratio of females to males was 5:1; the highest rates among women were observed in those who were pregnant and the lowest rates in those who were unmarried. Loudon and Greenhalgh pointed out that the patients studied represented a self-selected sample of the population which may result in an observed lower prevalence of infection than that which actually existed in the total community.

These studies illustrate an old and important approach to the study of the natural history of disease—an approach summarized so eloquently by Pickles³¹ who wrote as follows: "Let me recommend as a hobby, particularly to those young men entering country practice, this observation of the natural history of epidemic disease. In an editorial on this subject in the *British Medical Journal* it is stated: 'Organized medical statistics and laboratory experimental epidemiology are not substitutes for the observation of nature, but ancillary means.' We country practitioners are in a position to supply facts from our observation of nature, and it is, I feel most strongly, our plain duty to make use of this unique opportunity."

CLINICAL MANIFESTATIONS

Dingle⁶ pointed out that one of the first steps in developing solutions to the present and future problems of disease and of maintenance of health is the clinical approach—"the ability to diagnose or to recognize and identify a disease in an individual person."

What is the clinical picture of urinary tract infection? Acute infection of the lower urinary tract is readily apparent when it is associated with the sudden onset of dysuria, frequency, urgency and vesical tenesmus. There is usually little or no elevation in body temperature. The peripheral leukocyte count is normal. The urine may appear grossly turbid or even bloody and, at times, a foul odor is noted. Microscopic examination of the urine reveals numerous white blood cells singly and in clumps, many bacteria and, occasionally red blood cells. It is usually impossible to determine whether the kidneys are involved.

The clinical manifestations of upper urinary tract inflammation including pyelonephritis are exceedingly variable. The patient may present with an acute illness characterized by flank or low back pain, chills, fever, nausea and vomiting in addition to lower tract symptoms. Physical examination may reveal tenderness in one or both of the costovertebral areas or flanks. The body temperature is usually elevated as is the peripheral leukocyte count. In addition to urinary abnormalities such as pyuria and bacteriuria, the sediment may contain numerous white blood cell casts. Blood culture frequently reveals the presence of bacteria during the acute phase of untreated pyelonephritis.

In sharp contrast to instances of "typical" acute pyelonephritis are those individuals whose presenting signs and symptoms do not immediately suggest urinary tract involvement. Obscure fever may be the sole manifestation of illness. In addition, there remains the problem of inapparent or subclinical infection which some authors believe is frequent and plays an important role in the subsequent development of chronic renal disease and hypertension.

DIAGNOSIS

Urine Culture

The most valuable aid in diagnosis of urinary tract infection is bacteriologic examination of the urine. The techniques employed in urine culture have been studied extensively during the past ten years. It is now established that urine samples collected from healthy individuals under aseptic conditions frequently contain a wide variety of bacteria. These include many gram-negative species, such as, *E. coli*, *Klebsiella-Aerobacter*, *Proteus* and *Pseudomonas* in addition to certain gram-positive species such as diphtheroids, streptococci and staphylococci. These organisms, which are commonly found in the distal urethra of normal individuals, are usually present in small numbers, i.e., less than 1000 per ml. of urine. In instances of typical infection, however, careful studies have shown that bacteria are present in large numbers, i.e., 100,000 or more colonies per milliliter of urine. The significance of urinary bacterial counts in the intermediate range is often doubtful. Repeated urine collections and cultures provide additional data and lend further strength to the final interpretation of contamination versus infection.

The manner in which urine samples are collected and handled is critical. Nurses¹⁰ as well as physicians¹⁷ studying collection techniques have pointed out that "clean-void" midstream samples obtained under supervision provide satisfactory specimens for bacteriologic examination without the need for catheterization. However small the risk of properly performed catheterization in terms of later infection, such risks are unnecessary.

In order to arrive at a meaningful bacterial count, a measured amount of uncentrifuged urine should be placed on a solid rather than in a liquid medium. It is important that the samples be kept under refrigeration until actual bacteriologic techniques are performed, since urine itself is an ideal culture medium permitting active bacterial multiplication. Specimens can be held at icebox temperature for several days if necessary.²⁷ Despite these precautions, cultures may fail to reveal the presence of large numbers of organisms in instances of clinically typical infection owing to a variety of special conditions.¹⁶ These include suppurative renal lesions which do not communicate with the collecting system, obstruction of the ureter on the side of the lesion, markedly low urinary pH (below 5.5), periods of rapid dilute urine flow and, commonly, suppressed growth due to the presence of antimicrobial drugs.

What organisms are usually encountered in samples collected from infected patients? The data of Loudon and Greenhalgh reveal that in a general practice setting *E. coli* was found in the majority of patients. Grossberg et al.,⁹ studying

all cultures submitted to the Johns Hopkins Hospital Laboratory during a two month period in 1957, pointed out that bacterial species isolated from infected patients varied according to the place of acquisition of infection. Community surveys comprising mostly simple uncomplicated infections yield mostly antimicrobial drug-sensitive *E. coli* and relatively few drug-resistant *Klebsiella-Aerobacter*, *Proteus* and *Pseudomonas* species. The latter are frequently found in hospital series composed of complicated infections in which instrumentation had been performed.

Other Tests for Bacteriuria

Several rapid screening procedures have been recommended in estimating whether or not a given urine sample contains large numbers of bacteria. These methods offer a tentative answer pending confirmation by cultural technics. In addition they may be useful in follow-up investigations of patients receiving medication to detect the presence of organisms that may ultimately grow poorly or not at all on artificial culture media due to the presence in the urine of inhibitory drugs.

The first of these screening methods employs the Gram stain. Kass¹⁶ showed that the presence of organisms in a Gram-stained smear of a drop of uncentrifuged urine was indicative of high bacterial counts on subsequent cultural examination in 80 per cent of the cases. Kunin²³ reported that routine microscopy of the unstained sediment provided another reliable means of rapid visualization of bacteria. Sediments were prepared from 10 ml. of freshly collected or properly stored samples and examined at a magnification of 430 times in diminished light. The finding of 10 to 100 or more bacteria per field was almost invariably associated with a high bacterial count (i.e., 100,000 or more colonies per ml. of urine) on culture.

Although the presence of pyuria is useful confirmatory evidence of urinary tract infection, its absence in the first or even second urine specimen examined does not rule out active infection. As pointed out by Loudon and Greenhalgh,²⁵ ". . . the number of pus cells seen is subject to many variables; for instance, the magnification and number of fields counted, the urinary output when the sample was collected, the rate of production of pus cells in the urinary tract, and the length of time since the sample was collected, because pus cells tend to stick to the side of the container and, later, to disintegrate. Thus, it is partly a matter of chance whether a single sample contains a large or small number of pus cells."

Pus cell casts in the urinary sediment in instances of urinary tract infection point to involvement of the kidneys. Failure to observe white cell casts in repeated samples does not, however, rule out pyelonephritis. It should be noted that prostatic concretions to which leukocytes are adherent may simulate casts of renal origin.

ASSOCIATED CONDITIONS

Studies of bacteriuria in a variety of clinical settings have provided useful new data as well as posed many unanswered questions. Recent developments include: (1) studies relating use of inlying catheters to subsequent bacteriuria and infection; (2) demonstration that bacteriuria in women during pregnancy is followed by an increased prematurity ratio among their offspring and that this sequence appears to be prevent-

able; and (3) re-evaluation of certain "high-risk" groups such as diabetic patients among whom it has been traditionally held that urinary tract infection is more frequent and severe than among nondiabetics.

Catheters and Bacteriuria

The evidence that catheterization of the urinary bladder may lead to serious urinary tract infection has been summarized in an editorial by Beeson³ and reviewed at length by Williams et al.³⁵ The latter authors state that "estimates of the incidence of these infections vary, but there is no doubt that they occur too often, and are the commonest variety of infection resulting from medical or nursing practices in hospitals. Much urinary infection is frequently accepted as inevitable . . . it is doubtful if this is so."

These comments were not intended to do away with catheters but rather to point out the hazards of instrumentation and to clarify indications for these procedures. Catheterization is not necessary to collect an adequate sample for routine urinalysis or quantitative bacteriologic examination. Nor should catheters serve as simply a convenient way to collect urine for diagnostic procedures such as urea clearance tests or to keep the bed dry in instances of vesical incontinence. The value of instrumentation in the management of urinary obstruction is obvious.

Risk of catheter-associated bacteriuria and its subsequent course has been studied in a variety of clinical situations as follows:

Turck and Petersdorf³² performed single catheterizations in a group of 100 ambulatory patients and found only 1 possible instance of subsequent persistent bacteriuria when subjects were tested 2, 4 and 6 weeks afterwards. The use of a catheter only once during the course of labor and delivery, however, has been shown in a controlled study²⁸ to increase significantly the prevalence of immediate postpartum bacteriuria. Single catheterization, particularly during the course of lengthy or difficult labor, further increases the risk of subsequent bacteriuria.⁴ Prevention of bacteriuria following lengthy labor may be accomplished by encouraging patients to void at regular intervals and by avoidance of bladder distention during labor.

The late effects of postpartum bacteriuria are uncertain. We are presently observing patients in whom immediate postpartum bacteriuria was demonstrated to learn how long organisms persist and how often such patients develop later clinical manifestations. Turck and Petersdorf are conducting a drug trial to test the value of antimicrobial therapy in preventing postpartum bacteriuria.

Kass's¹⁷ observation that bacteriuria was almost invariably present within 4 days in patients following the use of indwelling catheters provoked renewed interest in the prevention of urinary tract infection. Ansell¹ in a recent review on catheter care pointed out some of the precautions necessary to avoid infection. He emphasized the need for careful attention to aseptic techniques, the use of small catheters, the merit of plastic catheters, closed drainage systems with a bactericidal agent such as 10 per cent formalin in collecting bottles, and a rapid flow rate of urine. There is little doubt that interest in technical improvements, attention to asepsis and the avoidance of cross-infection will prevent more infection and disability than increased use of antibacterial drugs.

What are the late effects of catheter-associated bacteriuria? Clarke and Joress⁵ concluded from a retrospective study of patients following the use of indwelling

catheters that bacteriuria did not necessarily persist if underlying factors such as obstructing lesions were removed and infections treated.

The subsequent course of bacteriuria associated with instrumentation was studied prospectively in a group of 21 women requiring vaginal hysterectomy and indwelling catheters.³⁴ High bacterial counts were observed in 4 of the 21 prior to surgery. After 2 or 3 days of constant bladder drainage, 14 of the remaining 17 exhibited bacteriuria. Four to 8 months following surgery and instrumentation and appropriate antimicrobial therapy, bacteriuria was present in 3 of the 21. Only 1 of the 3 was asymptomatic. Thus, under these conditions, there was only 1 instance of possible subclinical urinary tract infection following 2 to 3 days of constant bladder drainage.

Bacteriuria and Pregnancy

The systematic search for bacteriuria among asymptomatic women during pregnancy has led to one of the most promising and exciting recent developments in preventive medicine. In a series of studies at the Boston City Hospital, Kass¹⁸ showed that the prevalence of bacteriuria during pregnancy was 6 to 7 per cent. Approximately 40 per cent of women with persistently high bacterial counts developed pyelonephritis during pregnancy or immediately following delivery. Those patients without bacteriuria and those in whom organisms were eliminated by antibacterial therapy did not develop infection. Further, it was observed that there was a higher incidence of prematurity and related infant mortality among offspring of women with persistent bacteriuria during pregnancy than among infants of mothers without bacteriuria.

The proposed link between bacteriuria and prematurity has been studied intensively by several groups of investigators. The results to date are not in complete agreement. Kaitz and Hodder¹⁴ did not observe an increase in prematurity in a small group of women with bacteriuria. Turck and co-workers³³ were unable to show a significant difference in risk of premature births in women with or without asymptomatic bacteriuria. On the other hand, the results of the Baltimore study by Henderson and her co-workers¹² confirmed Kass's findings relating bacteriuria during pregnancy with an increased risk of prematurity.

Additional studies in a variety of population groups are needed. Undoubtedly prematurity and related infant mortality are due to a combination of factors and the extent to which bacteriuria and urinary tract infection are causal or contributory remains to be fully demonstrated. Turck and his co-workers suggest that a reasonable procedure based on available data is systematic search for bacteriuria and its elimination by antimicrobial agents in so-called "high-risk" groups (those in lower socio-economic strata, particularly nonwhite patients).

The long-term effects of urinary tract infection during pregnancy are not known with certainty, since data based on the careful follow-up of groups of infected women and suitable control subjects are not available.

Bacteriuria and Urinary Tract Infection Among Patients with Diabetes Mellitus

Beeson² commented that urinary tract infection is more frequent in diabetics than in nondiabetics, although precise data on this are lacking.

He cited the study of Harrison and Bailey in which they found a higher frequency of bacilluria and pyuria in patients with diabetes mellitus compared to a control group. In addition, he reviewed the serious nature of urinary tract infection in diabetic patients attending the George F. Baker Clinic in Boston.

These older studies are subject to criticism chiefly because they are based on poorly defined diabetic populations as well as comparisons with large series of autopsied individuals. Most retrospective studies on complicating illnesses in diabetic patients have limited value for their data represent an accumulation of what has happened to those who survive long enough to be included in a particular study and who are ill enough to be under medical care. A study of diabetes mellitus of 20 years' duration, for example, includes a highly selected sample of diabetic patients, not at all representative of diabetes mellitus in general.

Recent reports by Huvos and Rocha¹³ and O'Sullivan et al.,³⁰ however, present data which indicate that the prevalence of significant bacteriuria was similar in groups of diabetic and nondiabetic persons.

The ultimate answer to the questions of the frequency and seriousness of bacteriuria and urinary tract infection in diabetic patients will evolve from a prospective description of a large well-defined cohort of diabetic individuals and a suitable control group observed for at least five or ten years. For example, we²⁹ have attempted to measure the incidence of bacteriuria and urinary tract infection among a group of 51 newly diagnosed ambulatory diabetic women under study for several years. On initial screening, four of the 51 showed significant bacteriuria. The incidence of bacteriuria in this group based on three consecutive annual surveys was 6 per cent, i.e., three new instances among 47 women who were initially free of bacteriuria—a lower figure than those reported in previous cross-sectional studies of clinic or hospitalized groups.

RATIONAL BASIS FOR TREATMENT*

The goal of the patient with urinary tract infection seeking medical help is relief of distressful symptoms. The physician can provide that relief and, in addition, may be able to prevent future disability. Management is, however, beset with uncertainties. The source of the infection is usually not apparent and there are conflicting views about the efficacy of numerous currently available drugs. Few studies have been performed comparing specific agents and suitable control preparations. Indeed, the extent to which urinary tract infection is a self-limited process which is capable of spontaneous resolution is unknown. Fenwick⁷ wrote in 1895 that "if pus appears [in the urine] as a result of a simple catarrh, it will probably subside after rest in bed, and the free exhibition of bland diluents, to which some form of alkali is added, hot fomentations being applied and opium if necessary." Therefore, it must be emphasized that

* Two excellent reviews on management of urinary tract infection are recommended: (a) Kass, E. H.: Chemotherapeutic and antibiotic drugs in the management of infections of the urinary tract. Am. J. Med. 18: 764, 1955. (b) Kleeman, C. R., Hewitt, W. L., and Guze, L. B.: Pyelonephritis. Medicine 39: 3, 1960.

disappearance of symptoms and signs per se is of little value since clinical improvement without complete eradication of infecting organisms may be followed by persistent bacteriuria and subsequent flare-up of infection.

The outcome of treatment of urinary tract infection depends on several factors. These include the responsible micro-organism, its sensitivity to antimicrobial agents, associated illnesses such as uncontrolled diabetes mellitus, underlying structural or functional defects, and tissue changes related to past protracted infection.

The data of Fry et al.,⁸ already cited, illustrate that most instances of acute uncomplicated urinary tract infection improve rapidly during initial therapy. The diagnosis in these patients was proven with microscopy and culture. Adults were given a five day course of sulfonamides. Clinical responses were described as "good" and repeat urine samples collected from 160 of the 172 patients originally treated revealed no pyuria or bacteriuria in 151 of the 160 tested. Follow-up study four to six years later of 125 persons who had not moved away and were available for testing showed that persistent urinary abnormalities were present in 19 (15 per cent) of the 125. Six of the 19 were men in whom specific urologic lesions such as urethral stricture or prostate enlargement were found. Recurrent cystitis without any obvious cause accounted for nine of the 13 females. There were only three instances of chronic pyelonephritis among the 19.

The large segment of the practice that moved away and was unavailable for later testing constitutes a major limitation in the final interpretation of these data. These findings do not, however, indicate a serious treatment problem or the occurrence of many serious late effects of acute uncomplicated urinary tract infection. Most authors agree that results are generally good in acute simple urinary tract infection, but cure rates in the recurrent or chronic disease are disappointingly low, about 10 per cent.²⁴

Ideally, the aim of antimicrobial therapy of urinary tract infection calls for prompt and complete eradication of offending organisms—those which are present initially as well as others which may appear during the course of therapy. This approach requires the use of bactericidal agents which ideally are convenient to administer, safe and effective. Unfortunately, streptomycin, a potent bactericidal drug, must be given parenterally, is occasionally responsible for toxic side effects, and is limited to short periods of effectiveness. Some of these difficulties may be offset by combining its use with other preparations such as tetracycline. On the other hand, data based on careful long-term studies are not available to show that this form of therapy is any more successful in prevention of serious renal damage than some of the simpler suppressive or bacteriostatic regimens in common use. The latter include, for example, sulfonamides and nitrofurantoin.

The best practical course is the selection by the practitioner of two or three drug regimens with which he should become familiar in terms of efficacy, indications, administration and toxic manifestations. The initial step in management is precise diagnosis—recognition of bacterial

infection and assessment of the circumstances under which infection occurs. For example, not every patient with dysuria is infected. Nor is the sole consideration in an infected patient the prompt use of a given drug. Many obstructive urological lesions are readily correctible and subsequent renal impairment depends on recognition of these predisposing causes of urinary tract infection, *not* on drug therapy alone. When medication is used it should be based upon sound bacteriological diagnosis. Most patients probably can be successfully treated for a first episode of acute uncomplicated urinary tract infection without sensitivity tests. Evaluation of any scheme of treatment depends not upon the clinical response alone; it should be made in conjunction with follow-up cultures obtained immediately following a course of medication and at several subsequent intervals. It is our practice to treat patients for at least two weeks and, if there is a good clinical response, re-culture the urine after an additional two or three days. If the bacterial count is no longer elevated and there is no return of symptoms, the patient is requested to return in a month for repeat studies. Follow-up cultures are performed at several three-month intervals thereafter. Any evidence of persistence or recurrence of infection calls for re-evaluation and possibly urological study in addition to further bacteriological investigation. The collection of urine samples for follow-up studies does not require a catheter. "Clean-void" midstream samples are quite suitable.

There is no convincing evidence that prophylactic antimicrobial therapy offers any protection to patients undergoing lower urinary tract instrumentation or surgery.²⁰ When and if such patients become infected, then the principles apply in management of urinary tract infection as already outlined.

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Bacterial Infections of the Skin and Syphilis

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BACTERIAL INFECTIONS

THE NORMAL human skin forms an excellent protection against bacterial infection. It is extremely difficult to produce experimental skin infections, for in addition to the presence of a pathogenic organism, other changes, perhaps more subtle than a mere break in surface continuity, are necessary before infection can occur. The skin surface is never sterile nor can it be made so without producing epidermal damage.

The surface lipid film and sebaceous secretions form a rich culture medium for some bacteria, and the normal skin flora is extensive and variable, depending not only on personal habits and cleanliness but also on climatic conditions and the degree of sweating. Regional variations are also important; thus in the axillae sweating and maceration support a resident flora different from that in the external ear where the culture medium is cerumen. It is important to differentiate these resident non-pathogenic organisms from those transiently acquired from the gut, nasopharynx or hands, which may be pathogenic though not necessarily giving rise to clinical infection.

The prevention, diagnosis and treatment of skin infections in practice depends on an understanding of these and certain other basic concepts. With chronic or recurrent infections the detection of underlying systemic disease may be of paramount importance, and the possibility of nasal carriage of the responsible organism should always be remembered.

Normal Protective Mechanisms

The majority of all bacteria, pathogenic or not, which alight on the skin surface die within a few hours due to various protective mechanisms. The intact skin is a physical barrier, though the ostia of sweat glands and hair follicles form breaks in it often leading to the localization of infection at these sites. Sweat when produced in normal amounts is bacteriostatic, owing to its acid pH,

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and may literally wash away bacteria. Lastly, substances essential for the growth of some bacteria may not be present on the skin surface.

The destruction of bacteria reaching the skin surface is predominantly dependent on two processes, one physical dehydration and the other chemical due to the presence of oleic acid in the surface film, each mechanism showing partial specificity for certain organisms.¹¹

Dehydration destroys the coliform organisms which die as rapidly on the skin surface as on a dry glass plate. If the skin is kept artificially moist, coliforms can persist for several weeks and for this reason they often colonize exudative eczematous lesions.

The beta hemolytic streptococcus is rapidly destroyed on both moist and dry skin, this more specific bactericidal effect being due to oleic acid present in large amounts in normal sebum and surface film. Streptococci can survive on the skin for long periods if the oleic acid is removed by solvents such as acetone, or in the presence of serum albumin which inhibits the bactericidal effect of oleic acid. Streptococci can thus readily invade, colonize and secondarily infect areas of exudative eczema but are rarely found on normal skin.

Pathogenic staphylococci are not affected by oleic acid and are less influenced by dehydration than the gram-negative organisms. It is not surprising, therefore, that more than 20 per cent of the population harbor pathogenic staphylococci on some portion of their skin surface.^{4, 15}

Factors Leading to Skin Infections

LOCAL. The initial lesion is usually a break in the skin surface, followed by exudation of serum which, in addition to inhibiting the oleic acid mechanism, forms an ideal culture medium for bacteria. For this reason patients with excoriated pruritic dermatoses often develop secondary bacterial infections. A macerated skin following excessive sweating also forms a good nidus for bacterial growth and probably accounts for the increased incidence of secondary infection in intertriginous areas. It is thought, though not proved, that epidermal ischemia whatever the underlying cause lowers the skin's "resistance to infection" and accounts for the frequency of infection in ischemic limbs.

SYSTEMIC. Recurrent skin infections occur in many debilitating systemic disorders and may be the presenting sign of the underlying process. The most striking example of this is diabetes mellitus. In one year, in the Dermatological Department in Sheffield Royal Infirmary, one of the authors (C.V.) was able to collect 11 cases of previously undiagnosed diabetes mellitus which presented with recurrent bacterial infections of the skin, and a further six presenting with monilial balanitis or vaginitis. Most patients with monilial balanitis and no mechanical cause are diabetics. Hepatic disease may be complicated by recurrent skin sepsis especially in alcoholic cirrhosis, which is so often accompanied by malnutrition. A single severe bout or recurrent episodes of skin sepsis may be the presenting symptom of blood dyscrasias, especially the leukemias and agranulocytosis.

Many other systemic disorders, especially those associated with alterations in the serum proteins, may be complicated by episodes of skin infection. Finally, it must be remembered that the patient on systemic steroids is just as likely to develop a skin infection as a systemic infection, and that any infection apparently minor in nature may rapidly become more serious.

Laboratory and Office Tests of Value

Whenever possible it is advisable to obtain a specimen for bacteriological investigation before starting antibacterial therapy. The technique of taking the swab is all-important. A dried-out swab which has merely been swept over the surface of a crusted lesion is worse than useless. Any crusts on the lesions should be removed and a little of the underlying exudate taken onto the swab. If immediate examination of the material is not possible, it may be placed in a tube of Stuart's transport medium. A point often overlooked is that the area to be swabbed must not be cleaned with an antiseptic. Many sterile swabs are due to neglect of this apparently simple and obvious fact.

Some of the simpler bacteriological investigations can easily be performed in the physician's office. Examination of a film made by smearing the swab on a microscope slide, air drying and staining with the Gram stain will often give valuable clues as to the nature of the infecting organism. Fuller bacteriological information requires the preparation of cultures of the offending organism. Even this may be carried out in the office with the use of the now readily available disposable blood agar plates. To determine sensitivities accurately, subcultures are required. Such techniques are best performed in a fully equipped bacteriological laboratory. However, simple examination of a stained film and straightforward culture will often yield all the information required.

Basic Principles in the Treatment of Skin Infections

The first requirement in treatment is the application of an effective antibacterial agent, which can reach the infecting organism in adequate concentration without further damaging the already injured skin. Autoinoculation of unaffected areas must be prevented during treatment and any underlying systemic or dermatological disorder recognized and dealt with as indicated.

Ideally, the selection of the appropriate antibacterial agent should await the results of bacteriological study, but in practice a delay of two days waiting for this information may not be justified and may occasionally be harmful. In chronic or recurrent cases it is obviously better to wait for results from the laboratory. In the more acute case it is often possible to make a very reasonable guess as to the infecting organism, on clinical grounds alone, or with the aid of the Gram stain, and from this point initiate intelligent therapy. Too much faith should not be placed on *in vitro* sensitivity tests. An organism may be reported as insensitive to a particular antibacterial agent *in vitro*, but this may not be true with regard to topical treatment where the concentration of the agent at the site of infection is very high. Sensitivity tests are reported with reference to the likely serum levels of antibiotic obtained after systemic administration, which are small fractions of the local levels reached by topical therapy using the same antibiotic.

With the increasing use of antibiotics, the problem of bacterial resistance looms larger, especially in hospital practice. The rapidly increasing number of antibacterial agents has eased this problem somewhat, though their very number makes the selection of an antibiotic in any particular case more complex. Many of the staphylococcal infections acquired outside hospitals are still due to organisms which are sensitive to bacitracin and neomycin and will often respond rapidly to the hydroxyquinolone agents. Streptococci are still almost always sensitive to penicillin and the

tetracyclines. *Pseudomonas pyocyaneus* is always a problem organism though polymyxin and neomycin will usually be effective. The problem of the resistant staphylococcus was partly solved by erythromycin, though there are now many staphylococci resistant to this antibiotic. However, it is available for topical use, and the increased local concentration which results renders it very valuable in the treatment of resistant staphylococcal infections of the skin. The newer penicillinase-resistant penicillins^{3, 7, 12, 20} have revolutionized the systemic therapy of infections due to resistant staphylococci but they are not as yet available for topical use. It may well be that their potential for epidermal sensitization will be the same as that of penicillin, thus precluding their use topically.

Probably the most important single factor in the selection of an antibiotic for topical use is its potential as a cause of epidermal sensitization. The sulfonamides are now rarely used because of their propensity to induce severe epidermal reactions.¹⁴ Likewise, topical penicillin has fallen into justifiable disrepute¹⁸ because of its high incidence of epidermal sensitization. Many better drugs are available for topical use which have little if any systemic use. The risk of sensitizing a patient to penicillin by the topical route should never be taken, as its value systemically is so great. Chloramphenicol, though a very effective antibacterial agent, sensitizes a high proportion of patients who use it topically¹⁸ and should no longer be used except in very exceptional cases. Neomycin used topically because of its limited systemic use, also sensitizes a proportion of patients.² Erythromycin and the tetracyclines are extremely useful both topically and systemically and their extremely low incidence of sensitization makes their topical use justifiable.^{2, 8, 31} Bacitracin is another antibiotic with limited systemic use which is effective topically and has a low incidence of sensitization.

Two other factors need to be considered: first, the antibacterial agent must be stable in a suitable base for topical application, and secondly, it should be cosmetically acceptable, though this is of minimal importance.

Despite their effectiveness and low incidence of epidermal sensitization, many of the older remedies have undeservedly fallen into disrepute because they are cosmetically unacceptable. Vioform (a halogenated hydroxyquinolone) has both an unpleasant odor and color. Potassium permanganate 1/10,000 stains clothing and skin, while the colors of Castellani's paint and gentian violet are somewhat dramatic. Two per cent silver nitrate in 50 per cent industrial spirit, perhaps the best agent for the prevention of local spread around infective lesions, stains both skin and clothing black, the latter permanently. Despite this all these agents are extremely useful, especially in the chronic or recurrent case, or where epidermal sensitization is a problem.

It is very important that the antibacterial agent reaches the site of infection. It is useless to treat a carbuncle with topical therapy; here systemic antibiotics must be administered. Conversely, systemic antibiotics are of little use in the superficial forms of folliculitis. Blisters must be opened and crusts removed so the antibacterial agent may reach the organisms in maximal concentration. The removal of crusts is usually easy if the area is soaked in Burow's solution, potassium permanganate

(1/10,000) or even sterile saline. The vexed question of epilation is still unsolved. In the axillary region the removal of hair makes the treatment less messy, but may not increase its effectiveness. In the scalp epilation is unnecessary, except in neglected cases of pediculosis capitis, where it may be helpful at least to cut the hair short in affected areas for purely practical reasons.

Prevention of autoinoculation of uninfected areas is best accomplished by frequent changing of underclothes, the use of a germicidal soap and the addition of a germicidal agent to the bath water.

The final clearing of recurrent staphylococcal infections nearly always depends on the recognition of the important part played by the nasal or perineal carrier state and its eradication.^{10, 15} Every patient with a staphylococcal infection, acute or chronic, should have a nasal swab taken at the time of the initial examination. If pathogenic staphylococci are isolated, the patient should be treated by the twice daily instillation of the indicated antibiotic ointment. After one month the treatment may be stopped and further swabs taken one week later. If necessary, treatment can then be repeated. Several courses of treatment are often required to eradicate the nasal carrier state and this part of the treatment must be carried out concurrently with the treatment of the skin infection itself. Many puzzling cases of chronic and recurrent skin infections will be cured by using this technique. It should also be remembered that the nasal carrier may not be the patient, but a member of his family. Nasal carriers of staphylococci often complain of minor nasal symptoms which frequently clear when the staphylococcus is eradicated.

Clinical Entities and Special Points in Their Therapy

A classification of the important bacterial infections is given in Table 1.

IMPETIGO. Though especially a disease of childhood, no age group is exempt. The lesions are superficial and bacteria are present only in the upper layers of the epidermis. The primary lesion, an erythematous macule, rapidly becomes pustular or bullous and moist, sticky crusts appear, covering an oozing surface. The lesions may vary from a few millimeters to many centimeters in size, and if untreated may persist for weeks. Complications such as septicemia, rheumatic fever and acute glomerular nephritis are rare, though not unknown.⁹ Such complications have led to the use of systemic antibiotics in this disease, and in extensive cases or those known to be of streptococcal origin systemic antibiotics are certainly justifiable.

Ritter's disease, or *bullous impetigo of the newborn*, starts with the development of extensive bullae in the first two weeks of life. These soon collapse and extensive crusting occurs. Rapid spread is the rule and if treatment is delayed, in contrast to ordinary impetigo, mucosal involvement and constitutional symptoms follow. Systemic antibiotics should always be used.

FOLLICULITIS, FURUNCULOSIS, BOILS AND CARBUNCLES. Superficial folliculitis most often affects the extremities (*impetigo of Bockhardt*). On the beard area, *pili incarnati* or *pseudofolliculitis* may cause confusion. In this condition, most common in the Negro, the hairs become bent and grow back into the epidermis, producing a foreign body reaction

Table 1. A Classification of the Common Skin Infections, Their Causative Organisms and Most Useful Therapy

DISEASE	SUBDIVISIONS	ORGANISM			TREATMENT	
		Streptococcus	Staphylococcus	Other	Systemic	Topical
Impetigo	Bullous Contagiosa Ritter's disease Furunculosis	Occasional " " " " " " "	Usual " " " " " "	In strap. cases " " Yes No	Tetracycline or neomycin.	
Folliculitis	Boils Carbuncles	" " " "	" " " "		According to sensitivity. Treat nasal carriers.	
Ecthyma		Frequent	Frequent	E. coli	Surgery may be required. Tetracycline, neomycin or bacitracin.	
Erysipelas	Always				Penicillin or tetracycline	
Chronic paronychia		Occasional	Candida Ps. pyoeyaneus		Nystatin + antibiotic. Castellani's paint.	
Otitis externa	Rare	Frequent	E. coli B. proteus		According to sensitivity.	
Hydradenitis suppurativa		Usual	Ps. pyoeyaneus	Tetracycline or penicillin J	According to sensitivity. Surgery or radiotherapy may be needed.	

which is easily mistaken for an area of folliculitis. Treatment consists of the careful removal of the affected hairs. The deeper forms of folliculitis may leave scarring after healing. Two clinically distinct entities should be mentioned. *Sycosis barbae* may lead to severe scarring (*lupoid sycosis*), and folliculitis around the hair line may lead to alopecia and scarring (*folliculitis decalvans*). These two special types are very resistant to local therapy though epilation and superficial radiotherapy often help.

The deepest forms of folliculitis are usually referred to as *furunculosis*, and boils and carbuncle are merely the extreme expression of this process. In all patients with chronic or recurrent attacks of these deeper lesions, underlying systemic disease and the nasal carrier state must always be carefully considered.

In the treatment of chronic or recurrent furunculosis, the older forms of therapy are frequently extremely valuable, as the organisms responsible are often resistant to the newer antibacterial agents. The hydroxy-quinolone derivatives are also very effective and painting around the lesion with 2 per cent silver nitrate in 50 per cent industrial spirit will often prevent spreading.

Boils and carbuncles always require systemic antibiotics and may need surgical treatment as well, though many will resolve with antibiotics alone, if given early in the disease. In both conditions the prevention of autoinoculation is best accomplished by painting the surrounding skin with an agent such as 2 per cent silver nitrate in 50 per cent spirit.

ECTHYMA. This may reasonably be considered as a deep form of impetigo, which often leads to scarring (in contradistinction to impetigo). Treatment is essentially the same.

CHRONIC PARONYCHIA. Most commonly seen in the housewife whose hands are frequently wet, it is also seen in workers handling sugar and in diabetics. The yeast, *Candida albicans*, is responsible for the majority of cases by the time they are seen, though the primary lesion is often a bacterial paronychia which becomes invaded by monilia and certain bacteria especially *Pseudomonas pyogenica*. The disease is characterized by a tender swelling at the base of the nail. Often a small amount of white or yellowish material can be expressed from beneath the nailfold. A physical sign of great value is discontinuity of the nailfold over part of the affected nail. This is doubly important because it may represent the primary lesions and the mode of access of the infecting organism, and secondly because no patient should be considered cured until the cuticle is reattached to the nail plate along its full length. The nails may become grossly distorted during the active phase of the disease, and it may be months before they return to normal. Treatment is simple. The area must be kept completely dry by rubber finger stalls and an ointment containing nystatin and a suitable antibiotic (often bacitracin) applied twice daily. It should not be pushed under the cuticle as this retards healing. Treatment is time-consuming, the average case taking at least 12 weeks for complete cure.

ERYSIPelas. This disease, now rare, may give rise to severe constitutional symptoms. In rapidly developing cases, bullae may form and cause confusion with severe contact dermatitis (especially poison ivy). The response of erysipelas to systemic penicillin is dramatic.

HYDRADENITIS SUPPURATIVA. Bacterial infection of the eccrine sweat apparatus is rare, while that of the apocrine glands is common. It occurs most frequently in the axillae, though the groins are also occasionally involved. The condition is remarkably resistant to therapy and, though local and systemic antibiotics may help, recurrences are the rule. When the infection is localized to one or two glands, systemic antibiotics followed by surgical excision carries the best hope of cure. Superficial radiotherapy (100 rads once a week for four weeks at 75 kv.) may be helpful, but in the stubborn case plastic surgery with total excision of the area and full thickness skin grafts offers the only hope of complete cure.

Secondary Infection of Pre-existing Dermatoses

Although almost any dermatosis may become secondarily infected (Table 2), the frequency of such incidents varies with each disease. The basic principles of therapy are the same as those of the primary infections. Topical antibiotics should be used in the acute phase. If systemic symptoms are prominent, then systemic antibiotics should be employed. Treatment of the underlying disease should be started as soon as the infection has subsided. Secondary infection is so common in seborrheic dermatitis that most dermatologists use antibiotics or chemotherapeutic agents routinely in the treatment of this condition. In patients with atopic dermatitis, insect bites or scabies, infection usually starts in intensely pruritic areas, following excoriation and exudation of serum. For some curious reason it is very uncommon to see secondary infection in contact dermatitis. Patients with flexural psoriasis, diaper rash and intertrigo often develop secondary infection but this is most commonly due to *Candida albicans*. In the female with candida intertrigo the possibility of candida vaginitis should be considered.

There is little information on the value of topical use of antibiotic steroid combinations in the treatment of infected eczema or dermatitis. Certainly, clinical impressions suggest that these combinations may be actively harmful in the treatment of impetigo and other primary infections. In one group of children with infected atopic dermatitis, treated by other physicians with antibiotic-steroid combinations without success, healing occurred rapidly with the same antibiotic alone (this presupposes that the therapeutic failure was not due to antibiotic resistance on the part of the infecting organism).¹⁹ In a second group of children with infected atopic dermatitis and symmetrical lesions, antibiotic alone was applied to one lesion and the same antibiotic plus a topical steroid to the

Table 2. Secondary Skin Infections

Very common	Seborrheic dermatitis
Common	Atopic dermatitis
	Scabies, pediculosis and insect bites
	Epidermophytosis
	Diaper rash
	Flexural psoriasis } Usually monilial
	Intertrigo }
Rare	Contact dermatitis
	Nummular eczema

other. In ten of these children, there was a striking difference in the rate of clearing of the two lesions, that treated with antibiotic alone clearing on the average at least three days earlier.¹⁹ The use of antibiotic alone does not seem to allow the underlying dermatosis to escape from control but a return to the usual therapy for the underlying disease must be made when infection has been cleared.

Chronic otitis externa deserves special mention. In many cases the primary lesion is an irritative dermatitis secondary to chronic middle ear discharge. This dermatitis then becomes infected by the organism responsible for the ear disease (often a gram-negative and resistant bacteria). Even if the skin infection is cleared, continuous reinfection occurs from the aural discharge. The best local therapy is a combination of polymyxin, bacitracin and neomycin applied as drops, but close cooperation with the otorhinolaryngologist is required at all stages. Seborrheic dermatitis accounts for the majority of the remaining cases and here, once the secondary infection has subsided, a return must be made to therapy for the underlying condition.

SYPHILIS

With the introduction of penicillin during World War II, the problem of syphilis started to diminish. Treatment was grossly simplified. The proper penicillin treatment schedules for management of syphilis in its various stages and types were determined from masses of well-kept records over long periods of time. Very few diseases have been so thoroughly investigated in regard to a given therapeutic agent.

The incidence of new syphilis diminished dramatically during the late '40's and early '50's. As a result, syphilis, as a disease, probably received less interest from the medical profession than it had for 300 years. From 1950-1960, large clinical centers might go an entire year with discovery of only one or two new cases of primary or secondary syphilis. Review of routine serological tests for syphilis revealed that there were so few cases of active, untreated syphilis detected by this means that it left serious doubt that the time and expense involved in routine serologic tests was worthwhile.^{1, 21} Syphilis, which had been recognized by clinicians as the disease which may mimic all other diseases, was being replaced by collagen diseases in this context.

The main problem which remained in syphilis was the interpretation of the positive serologic test for syphilis. This still remains practically a specialty within itself. The development of more reliable and specific tests for syphilis has been a large advance in management of the problem of a positive serology. Now one can get close to 100 per cent accuracy in the serologic diagnosis of syphilis with such tests as TPI (treponema immobilization test), RPCF (Reiter protein complement fixation test), FTA (fluorescent treponemal antibody test). There are also others which use the specific antigen derived from *Treponema pallidum*. The biologic false-positive reactor can be determined more readily and with greater confidence than ever before.

Some facts gathered by the Department of Health, Education and Welfare are worth mentioning at this time.^{6, 16, 17} There are now 1.2 million cases of syphilis in the U.S.A. In 1961 there were 4.4 cases of primary and secondary syphilis per 100,000 population and 60,000 cases of syphilis are being added each year in the U.S.A. There was a 50 per cent increase in primary and secondary syphilis in the U.S.A. from 1960 to 1961. The death rate from syphilis was 1.8 per 100,000 population in 1961.

An alarming fact is that a large number of cases of early syphilis are going undetected. Many of these affected persons will not only pass the infection on to others but will in the years ahead develop severe incapacitating and fatal tertiary complications of syphilis.

The marked rise in the incidence of early syphilis is shocking. In our own clinic area we are seeing ten times the number of cases of early syphilis that we saw three years ago. Many of these cases are in male homosexuals—an international finding.^{5, 6, 8} This group is more active sexually and contacts are harder to trace. In addition, primary syphilis in this group frequently appears in extragenital areas (e.g., anus, mouth). Extragenital chancre are very likely to be misdiagnosed.

Another factor in the increasing incidence of syphilis is the decreasing use of penicillin in adults because of the high incidence of unpleasant reactions to the drug. This, of course, includes acute, fatal reactions. Previous widespread and indiscriminate use of penicillin no doubt suppressed or cured syphilis in many individuals.

An interesting and, recently, more frequent error is with the patient who is treated with penicillin for an "upper respiratory infection" by his physician. The patient develops a Herxheimer reaction from penicillin in four to 12 hours consisting of an acute flare-up of his syphilitic lesions along with fever. The physician frequently interprets this as a "penicillin reaction," stops the drug immediately and, unfortunately, well before the patient has had adequate therapy for syphilis.

Recognition of Early Syphilis

A. Clinical

1. Penile lesion in male; primary lesion in female rarely noticed by patient
2. Regional lymphadenopathy (nodes firm, nontender, nonsuppurative)
3. Prolonged general malaise and low grade fever
4. Recurrent "upper respiratory infection"
5. Hoarseness
6. Alopecia (particularly scalp, patchy or diffuse)
7. Papular lesions on palms and soles
8. White patches on mucous membranes
9. Generalized skin lesions (relatively asymptomatic)

The diagnosis of syphilis will rarely be made if it is not included in the differential diagnosis when any of the above clinical findings are present. Conversely, the diagnosis once suspected is quite simple to confirm (darkfield demonstration of *T. pallidum* and/or positive serologic tests for syphilis).

B. Laboratory

1. Darkfield positive (experienced person should perform)
2. Serologic tests for syphilis
 - a. May be negative in early primary stage.
 - b. Always positive in secondary stage.
 - c. Specific tests such as TPI, RPCF and FTA may be negative in the very early stage of secondary syphilis whereas nonspecific tests such as the routine precipitation and complement fixation tests with non-specific antigen (Wassermann, Kahn, Klein, etc.) should be positive.
 - d. After the very early stage of secondary syphilis (3 to 6 weeks) the specific tests using treponemal antigen are extremely reliable. These tests (RPCF, TPI, FTA) will be done by State and Federal laboratories if proper requests are made. Also, many local clinical labora-

tories are now adopting the RPCF and FTA specific tests because they are relatively inexpensive. These specific tests are rarely needed unless the nonspecific tests are positive and the interpretation of the positive, nonspecific test is in doubt.

3. Spinal fluid tests for syphilis

- a. Nonspecific antigen tests are quite reliable.
- b. Rarely need to use specific antigen tests.
- c. Cell count and protein concentration are useful in detecting *active* infection in central nervous system.
- d. Not necessary in primary and secondary syphilis.

If syphilis is not discovered in the early stages of the disease, the individual may develop severe, destructive lesions in any of the organs some three to 50 years after the original infection. However, it is well known that the majority of patients with untreated syphilis will live a relatively normal life without any major involvement of central nervous system, heart or great vessels, viscera, bones or skin. In fact, some of these individuals may spontaneously revert to negative serologic tests for syphilis without ever having had specific therapy. The latter should be stated parenthetically, because the incidence of severe late destructive changes is still very high, probably over 25 per cent in untreated syphilis.

Many persons who have had untreated syphilis for two to three years or more will maintain, indefinitely, a positive serologic test for syphilis (specific and nonspecific tests). It should be remembered that *adequate* penicillin therapy will have little or no influence on these persistent, positive serologies. One of the common mistakes is to keep treating the patient with penicillin as long as he shows a positive serologic test.

More than adequate statistical evidence and prolonged clinical experience have shown that 9,000,000 units of penicillin given over a 10 to 14 day period give results which cannot be improved by additional penicillin at any time in the future, or by bismuth, arsenicals or fever therapy. One should bear in mind the possibility of reinfection with syphilis, in which case penicillin therapy is again needed. Treatment of syphilis with amounts of penicillin greater than this suggests emotional rather than rational judgment. There is no documentation of penicillin resistance on the part of *Treponema pallidum*.

The role of the spinal fluid test is less clear now than it was 20 years ago when arsenicals and bismuth were the only useful drugs in management of syphilis. Certainly in primary and secondary syphilis there is no reason to obtain spinal fluid. In a patient with subjective or objective signs of central nervous system disease, a spinal fluid tap would probably be indicated whether or not syphilis was primarily suspected.

Many of the positive serologic tests for syphilis will be in persons with *late latent syphilis*. This means that they have probably had syphilis for many years but do not show any clinical signs of the disease. The only positive evidence of disease is the positive blood test. Some of these subjects may have laboratory evidence of syphilis of the central nervous system (positive complement fixation, increased cell count, increased protein, or evidence of abnormal protein) without clinical evidence of central nervous system disease. These cases are classified as asymptomatic neurosyphilis. Adequate treatment for this phase of syphilis is no

different from the treatment for late latent syphilis. Therefore, the examination of spinal fluid in the late latent syphilitic becomes more a matter of academic than of practical importance.

Primary syphilis and secondary syphilis respond to 6,000,000 units of penicillin given over a ten day period (aqueous procaine penicillin 6,000,000 u. q.d. \times 10, or procaine penicillin with aluminum monostearate in oil 1,200,000 u. every other day \times 5). Also, bicillin 2.4 to 4.8 million units can be given in one injection. This is adequate for cure of the infection in early syphilis. It has the advantage of not requiring regular attendance on the part of the patient to complete a course of therapy. A disadvantage is the prolonged course of any drug reaction the patient might have with a long-acting penicillin. Briefly, one should again point out the necessity of checking the history of the patient regarding penicillin sensitivity and skin testing where necessary. Special care should be taken in giving penicillin to an atopic individual because of his propensity to experience fatal reactions to penicillin. If the patient should be found to be, or suspected to be, allergic to penicillin, one may substitute erythromycin 2 gm./day to a total of 20 to 40 mg.

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Brain Abscess

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WITH THE introduction of effective antibacterial chemotherapy, the entire aspect of intracranial suppurative disease has been profoundly altered. Some of these diseases, e.g., intracranial thrombophlebitis, bacterial meningitis and certain cases of extradural abscess, can be managed entirely, and successfully, by the use of antibiotic medication; in others, e.g., subdural empyema and cerebral abscess, the use of antibiotics has greatly facilitated the treatment, which is still ultimately surgical. In specific relation to brain abscess, the most gratifying effect has been on the mortality rate. At the Massachusetts General Hospital,² for example, the mortality dropped from 80 per cent in the period 1936–1940 to 34 per cent in the period 1946–1950; and in a series from the Radcliffe Infirmary, Oxford, from 46 per cent (1938–1942) to 29 per cent (1943–1948), although the principles of surgical treatment of brain abscess were much the same throughout both periods.¹⁶ Interestingly, the incidence of brain abscess has not fallen correspondingly. In fact, in the Oxford series the incidence was actually higher during the antibiotic period. Brain abscess remains a serious matter in other respects as well. Although the mortality has been sharply reduced, it is still far from insignificant. Problems in the recognition and management of brain abscess remain formidable. Furthermore, the patient who survives surgical eradication of the abscess may be left with permanent neurological disabilities.

With the exception of a relatively small number of cases in which infection may be introduced from the outside (compound fractures of the skull, intracranial operations), the occurrence of a brain abscess is always secondary to a focus of suppuration elsewhere in the body. Appreciation of the various forms of suppurative foci which underlie abscess and the portals by which the organisms reach the brain is an essential requirement for the early recognition of brain abscess and its effective management. An understanding of these basic facts is important not only in relation to brain abscess, but to other intracranial suppurative diseases, such as epidural and subdural empyema and meningitis, with which abscess may be associated and from which it has to be distinguished. A considerable portion of this presentation will therefore be devoted to a discussion of the mechanisms involved in the genesis of brain abscess and related disorders.

Chronic middle ear infection and mastoiditis are the most common sources of brain abscess. In the preantibiotic era, these sources accounted for somewhat more than half of all the cases,⁵ and even now they represent the most important causes.^{2, 16} In these cases the abscess is most frequently found in the temporal lobe, next most frequently in the cerebellum, occasionally in other parts of the brain or in more than one of these locations. The precise location of the abscess will depend on the mode of spread of the infection.

One method of spread is by direct extension in which the roof of the tympanic cavity or mastoid bone becomes the seat of an osteomyelitis, with subsequent necrosis of bone and perforation. The dura and then the leptomeninges become locally inflamed, covered with exudate and adherent to the infected bone and to the brain respectively. Penetration of these membranes by infected material establishes a suppurative focus in the inferior part of the temporal lobe. A similar sequence of events affecting the posterior wall of the mastoid antrum will lead to an abscess in the cerebellum. In adults, the abscesses formed in this manner are found more often in the temporal lobe than in the cerebellum, in a ratio of about 3:2. The fact that cerebellar abscess from direct extension is relatively more frequent in children may be explained by the observation that the roof of the tympanic cavity is thicker and less brittle in children than in adults.⁵

The pathological events which may complicate otitis media and osteomyelitis of the overlying bone need not conform to the sequence outlined above. Any of the anatomical strata traversed by the pyogenic organisms may become the site of a suppurative focus; an epidural or subdural abscess or a bacterial meningitis may all have the same origin, and on occasion one or more of these may occur together with brain abscess. The factors which determine the particular form of the infectious process are not understood.

An alternate mode of spread of infection is along the walls of veins. The diploic vessels of the calvarium as well as major veins from the inner ear, nose and sinuses drain into the dural venous sinuses, which also receive blood from the dura, leptomeninges and brain. Thrombophlebitis of the pial veins and dural sinuses provide the mechanism for the formation of a brain abscess by blocking normal blood flow and infarcting brain tissue which is thus rendered more vulnerable to invasion by the infectious material. Experimental data in animals suggest that infarction of tissue is a most important factor in the pathogenesis.

A number of authors^{6, 10, 17} have shown that injection of bacteria into normal brain tissue will rarely create an abscess and that, in order to do so, one must first damage the tissue or inject the organisms with a medium in which they are growing. The role of venous infarction in the pathogenesis of brain abscess in humans is difficult to evaluate. It is undoubtedly a factor in certain instances,¹² but whether it occurs in all cases cannot be determined.

The intimate anatomical relationship between the lateral (transverse) sinus and the cerebellum explains the frequency with which this portion of the brain is infected via the venous route. The spread along venous channels also explains how an abscess may sometimes be formed in the frontal or parietal lobes at a considerable distance from the primary focus of infection in the middle ear.

Infections of the nasal cavity and its accessory sinuses constitute important sources of cerebral abscess, although considerably less frequent ones than the middle ear and mastoid. The sinuses most frequently implicated in brain abscess are the frontal and sphenoidal, and, with few exceptions, the abscesses derived from them are in the frontal and temporal lobes respectively. The infection reaches the brain in much the same manner as it does from an otitis media. In some cases, an osteomyelitis and necrosis of the sinus wall occurs, from which the infection spreads by direct extension; in others, the infection extends along the veins opening into the cavernous sinus, with or without an antecedent osteomyelitis.

Another major category of brain abscesses are *metastatic*, i.e., abscesses which arise from a source of infection remote from the cranial contents. An indication of their frequency can be obtained from the figures compiled at the Mayo Clinic. Between the years 1915-1945 autopsy examinations were performed on 104 patients with metastatic abscess of the brain; these constituted 0.6 per cent of all autopsies and about one-third of all brain abscesses.⁸ These figures are in general agreement with those of other large series.^{4, 5, 15}

The most important sources of metastatic brain abscess are the *lungs*, the *pleura* and the *heart* (including cases with congenital heart disease), but in addition, occasional cases will be encountered in association with infected pelvic organs, skin or tonsils, abscessed teeth, and with osteomyelitis of noncranial bones. A detailed account of this subject is contained in the review of Gates et al.⁸ According to these authors, 44 per cent of metastatic brain abscesses arise from chronic suppurative diseases of the lungs and pleura. These diseases comprise bronchiectasis, lung abscess and empyema; bronchiectasis is the most frequent of these disorders, but often they occur in combination. A nontuberculous abscess of the brain may occasionally be associated with fibrocaceous pulmonary tuberculosis, presumably because of an associated bronchiectasis. Abscesses secondary to the pleuropulmonary disease are multiple in over 40 per cent of cases; they affect the frontal, parietal and occipital parts of the brain with about equal frequency, but only rarely the temporal lobes or the cerebellum. These features set them apart sharply from the abscesses of middle ear and sinus origin.

The heart is an important source of metastatic brain abscess and may be implicated in two distinct ways: (1) fragments of infected vegetations

from the heart valves may lodge in cerebral vessels and (2) congenital defects may permit a short-circuiting of the pulmonary circulation, allowing infected emboli to reach the brain (paradoxical embolism).

A careful distinction has to be drawn between the neuropathological effects of *subacute* and *acute bacterial endocarditis*. Subacute bacterial endocarditis, i.e., the type caused by the implantation of viridans streptococci on valves previously damaged by rheumatic fever, or on a patent ductus arteriosus or ventricular septal defect, very seldom, if ever, gives rise to brain abscess. The cerebral lesions of subacute bacterial endocarditis are due to the embolic occlusion of vessels by fragments of vegetations and bacteria, which cause infarction of brain tissue and a restricted inflammatory response around the involved blood vessels and in the overlying meninges. The spinal fluid contains moderate numbers of polymorphonuclear leukocytes and frequently red cells as well, but the sugar content is never lowered and suppuration in the brain or in the subarachnoid space does not occur. It is theorized that the chronicity of the viridans infection allows the nervous tissue to develop an immunity to the organisms. On the other hand, acute bacterial (ulcerative) endocarditis, i.e., the type which is commonly caused by the *Staphylococcus aureus*, hemolytic streptococcus or the pneumococcus, which runs a fulminating course and may involve normal valves, very frequently gives rise to multiple small abscesses in the brain, as it does in other organs of the body.

Although an instance of brain abscess complicating *congenital heart disease* was described by Farre⁷ as long ago as 1814, and isolated cases, usually discovered at necropsy, have been reported sporadically since then, it has been only in the past decade or two that this complication has been generally recognized during life and its frequency appreciated. In recent reports it is estimated that about 5 per cent of cases of congenital heart disease are complicated by brain abscess.^{3, 14} It should be emphasized that these abscesses are usually solitary; this fact, coupled with the realization that the underlying cardiac abnormality can often be corrected surgically, makes the early recognition of brain abscess in congenital heart disease a matter of great practical importance.

Brain abscess may be associated with congenital heart disease at any age, but for some reason it is rarely seen before the third year; infarction of the brain due to thrombosis of arteries or veins is the usual neurological complication in the first two years of life. The tetralogy of Fallot is by far the single most common anomaly associated with brain abscess, but any type which allows the recirculation of venous blood through the systemic circulation may be implicated. The filtrating effect of the lungs is thus avoided, and pyogenic bacteria or infected emboli from a variety of sources may gain access to the brain, where, aided by the effects of venous stasis and perhaps of infarction, an abscess is established. At least this is the current theory of their mechanism. Bacterial endocarditis is absent in these cases and cannot be incriminated in the pathogenesis.

Having indicated the major sources of brain abscess, it should be pointed out that in a relatively small proportion (5 to 15 per cent in various large series) a primary focus of infection cannot be found. This is particularly true of cases of abscess with congenital heart disease, and to a lesser extent of other forms of metastatic abscess. In some cases the source of infection only comes to light after the brain abscess has been

recognized and successfully treated. In others, the primary infection may resolve and leave no trace by the time the brain abscess becomes manifest. According to Pennybacker,¹⁶ the prognosis in the latter type is generally favorable insofar as the resolution of the primary infection indicates an organism of relatively low virulence and the abscess is commonly a chronic encapsulated one, which lends itself to surgical removal.

PATHOLOGICAL FEATURES

When the infection reaches the brain by direct extension, the abscess is regularly found adjacent to the primary focus, which is usually marked by an osteomyelitis and adherent, inflamed meninges. Abscesses which result from the spread of infection along veins are located a short distance from the primary site, in the distribution of the nearest major venous sinus. For example, a cerebellar abscess resulting from otitis media is almost always localized to the ipsilateral anterior superior portion of the cerebellar hemisphere (see Fig. 1); veins from this part of the cerebellum pass laterally to the segment of the transverse sinus which receives deep veins from the middle ear. Metastatic abscesses take the form of single or multiple suppurative foci in an arterial distribution, most commonly of the middle cerebral artery.

Once the pathogenic organisms reach the neural tissue, regardless of their source, an inflammatory exudate forms, dominated by clusters of polymorphonuclear leukocytes surrounding the vessels. The affected brain tissue undergoes necrosis. The center of the lesion is occupied by bacteria, necrotic brain tissue and leukocytes in different stages of disintegration. Surrounding the necrotic tissue are edematous parenchyma, macrophages, astroglia, microglia and many small veins, some of which show endothelial hyperplasia and are filled with fibrin and cuffed with polymorphonuclear leukocytes. At this stage, which is rarely observed post-mortem, the necrotic tissue is poorly circumscribed and tends to spread by a coalescence of inflammatory foci. To this local suppurative encephalitis or immature abscess the term cerebritis is often loosely applied.

Soon the intensity of the reaction begins to subside, and the infection tends to become delimited. The center of the abscess takes on the character of pus, i.e., a liquefied mass of fibrin and neutrophils in various stages of degeneration; at the periphery, fibroblasts proliferate from the adventitia of newly-formed blood vessels to form a wall of granulation tissue, which is readily seen within 2 weeks of the onset of the infection. As the abscess becomes more chronic the granulation tissue is replaced by collagenous connective tissue. The inner layer of this wall is made up of degenerating neutrophils and fibrin, and the outer fibrous capsule merges with a zone of altered tissue where lymphocytes and plasma cells, some lying free and others cuffing the vessels, hyperplastic astrocytes, small foci of necrosis, thrombosis of small vessels and edema of the white matter are principal changes. The latter findings emphasize the fact that, although the abscess appears to be delimited and in a reparative phase, there is still evidence of infection remote to it. Eventual occlusion of the more peripheral vessels could conceivably result in extension of the abscess toward the satellite necrotic zones. It has also been noted, in both experimental animals and humans, that the capsule of the abscess is not of uniform thickness, frequently being thinner in its deeper portions. All of these factors account for the propensity of cerebral abscesses to spread deeply into the white matter, to produce daughter abscesses or a chain of abscesses, and to culminate in a catastrophic rupture into the ventricles.

In the past, the bacteriological aspects of brain abscess were largely academic, except for the common belief that the process of encapsulation was influenced by the type of organism.^{1, 9} This supposition has not been borne out clinically or experimentally.^{6, 8} With the advent of the antibiotic era, bacteriological considerations have assumed new importance. In the local and systemic treatment of brain abscess, antibiotics have an important role, and their appropriate use depends on accurate bacteriological studies.

The organisms responsible for brain abscess are remarkably diverse. The abscess may contain only a single organism, but more frequently several organisms are present. In abscesses derived from the middle ear and the paranasal sinuses, the most common organisms (and fortunately the most sensitive) are staphylococci, streptococci and pneumococci, but various anaerobic strains of streptococci and coliform, diphtheroid and fusiform bacilli may also be present.

Metastatic abscesses are caused by an even greater variety of pathogens. The exciting organism of the abscess usually reflects the organism or organisms of the primary focus. Virtually every bacterial inhabitant of the throat and lungs is a potential causative agent. Anaerobic streptococci are commonly found in the abscesses complicating congenital heart disease, but again, a wide variety of organisms, frequently multiple, may be found. Abscesses arising from acute bacterial endocarditis yield a relatively limited number of organisms which have already been enumerated. Unusual instances of abscess may be due to the typhoid bacillus, *Entamoeba histolytica*, actinomycetes, blastomycetes, aspergillus, coccidioides, cryptococcus, nocardia, *Candida albicans* and a myriad of other bacilli, fungi and parasites.

In a small number of cases, the pus from an abscess will be sterile. Blood cultures show a growth only in rare cases associated with septicemia. As a rule, the spinal fluid yields no growth unless the abscess is associated with purulent meningitis, which results from the rupture of an abscess into a ventricle, or from development of both a meningitis and an abscess from a common source. In these cases it is possible that more than one organism may be cultured from the spinal fluid, a situation which should always alert one to the presence of an underlying abscess.

FEATURES OF CLINICAL AND DIAGNOSTIC IMPORTANCE

A reconstruction of the history of patients with cerebral abscess discloses that the initial symptom of intracranial infection is most often headache. This usually intrudes itself at a time when the attention of both physician and patient are focused on some aspect of the primary infection. The appearance of headache, or any neurological symptom which cannot be explained by the primary infection, should alert the physician to the danger of an abscess. Or, in the patients without an obvious focus of infection, the headache may come on abruptly, on a background of mild, general ill health or congenital heart disease. Other

presenting symptoms, roughly in order of their frequency, are drowsiness, confusion and stupor, generalized or focal seizures, nausea and vomiting, and focal motor, sensory or speech disorders.

In about half the patients the headache is more severe on one side, in which case it indicates the side of the abscess. The headache increases in severity as the disease progresses and is accompanied by other signs of increased intracranial pressure, viz., nausea and vomiting, depression of the state of consciousness and papilledema, the latter sign being a late development in about half the cases. Localizing neurological signs are present sooner or later in almost all cases, but, like papilledema, they occur relatively late in the course of the illness and one should not wait for their development in order to establish a diagnosis of brain abscess.

The nature of the focal signs will, of course, depend on the locality of the abscess. In frontal lobe abscess, these signs usually take the form of hemiparesis, focal seizures and, with involvement of the dominant hemisphere, aphasia, grasping and sucking reflexes or variants thereof may also be present. An upper homonymous quadrantanopia is characteristic of a temporal lobe lesion and, if the dominant lobe is affected, Wernicke's aphasia (a misuse of words and an inability to read and write and to understand spoken commands) or a lesser degree of aphasia, particularly a failure to name common objects, may be present. An abscess of the parietal lobe, right or left, will show a homonymous hemianopsia or visual inattention, an impairment or abolition of optokinetic nystagmus and a cortical sensory syndrome (loss of position sense and discriminative sensation with relative preservation of vibration, touch and pain sense.) In addition, a lesion of the dominant parietal lobe will result in an impairment of language function, whereas patients with a lesion of the nondominant lobe may show anosognosia as well as neglect of the opposite side of the body and of space. The main manifestation of an occipital lobe lesion will be a homonymous hemianopsia. Cerebellar abscesses will give rise to the characteristic disorders of gait and coordination referable to that organ. Often the focal signs tend to be obscured by the patient's drowsiness, stupor and general ill-health, and one must be persistent in attempting to elicit them.

It should be emphasized, if it is not apparent from this brief review of the clinical features, that the picture of brain abscess is far from stereotyped. Whereas headache may be the most prominent feature in most patients, seizures or certain focal signs may predominate in others, and a considerable number of patients will present with the signs of increased intracranial pressure. Attempts have been made by some authors to divide the clinical course of brain abscess into three or four distinct stages, with the implication that these follow one another in a predictable sequence. Such a concept does not coincide with our experience. In many instances the symptoms evolve swiftly, new symptoms being added day by day. In patients with metastatic brain abscesses of known origin, the duration of the illness, from the first symptom to the time of death, is five to 14 days in half the cases.⁸ Although a tempo of evolution of such rapidity is not universal, it does illustrate the speed with which this disease process can run its course.

Other cases will evolve more slowly, and a small number will run such an indolent course that a mistaken diagnosis of neoplasm is made. Another impressive feature is the unpredictability with which the symptoms of brain abscess may evolve; this is particularly true in children. Thus a patient whose clinical course seems to have stabilized or is advancing very slowly, may in a matter of hours or within a day reach a most advanced or irreversible state. All these features need to be taken into account in the management of the patient.

Usually the patient with brain abscess shows a moderate temperature elevation to between 100 and 102° F. and a polymorphonuclear leukocytosis, but occasionally a particularly chronic, well encapsulated abscess may exist without any fever. The cerebrospinal fluid pressure is moderately increased (200 to 300) in the average case, and may be very high in advanced cases. In the absence of a generalized meningitis, the cell count ranges from 20 to 300, occasionally higher or lower, with 10 to 80 per cent neutrophils. In a few cases there are only lymphocytes, and very occasionally there are no cells at all. The protein content is usually elevated, at times over 100 mg. per 100 ml., but the sugar is never lowered unless there is a concomitant suppurative meningitis.

Röntgenography of the chest and skull and electroencephalography are so readily available and so undisturbing to the patient that they must always be performed as a routine extension of the physical examination. The importance of skull films in detecting disease of the middle ear, mastoid and sinuses and a shift of the pineal gland is obvious. In infancy and early childhood, a separation of the cranial sutures may be the most informative sign of increased intracranial pressure. The electroencephalogram is a valuable aid in the localization of cerebral abscess, usually showing a focus of high voltage slow activity over the abscess area. In most cases, special diagnostic measures have to be employed to confirm the diagnosis. Scanning the brain after the intravenous injection of radioactive arsenic or copper may prove useful in detecting an abscess, but this technique is not available everywhere. Carotid angiography is usually a satisfactory method for localizing an abscess in the presence of increased intracranial pressure. Matson and Salam¹³ have made the point that in cyanotic congenital heart disease, with a high degree of polycythemia, angiography increases the danger of vascular occlusion, and they advise that air studies be used under these circumstances. Another commonly employed measure, introduced by Kahn,¹¹ in 1939, consists of the injection of 2 to 3 ml. of Thorotrast in the abscess cavity at the time of initial aspiration. This radiopaque substance is taken up by phagocytes in the wall of the abscess, so that the size of the lesion in response to treatment can be observed.

Differential Diagnosis

In the differential diagnosis of brain abscess, the following disorders have to be considered: epidural abscess, subdural empyema, cerebral thrombophlebitis, focal embolic encephalomalacia due to subacute bacterial endocarditis, acute necrotizing hemorrhagic encephalopathy, neoplasm, and occasionally massive ischemic infarction.

An *extradural abscess* rarely reaches sufficient proportions to cause in-

creased intracranial pressure or focal neurological signs. Irregular fever, local headache and tenderness over the affected region and mild pleocytosis of the spinal fluid are its main manifestations. It can often be treated effectively by antibiotics alone.

Subdural empyema is a highly lethal complication of frontal sinusitis and osteomyelitis, and rarely of otitis media. The subdural pus accumulates over the frontal lobe, and in rapid sequence the patient develops high fever, stiff neck, and hemiplegia. The spinal fluid is sterile, but under high pressure and contains several hundred or a thousand or more neutrophils. The exceedingly rapid tempo of evolution, the findings on spinal fluid and angiographic or diagnostic burr-hole examination help to distinguish subdural empyema from brain abscess.

Intracranial thrombophlebitis is a frequent complication of suppurative meningitis, usually manifesting itself four to ten days after the onset of meningitis by a burst of seizures, focal neurological signs and a recrudescence of fever. In other cases the lateral, cavernous or superior longitudinal sinuses are affected by spread of infection from the middle ear, skin of the face, or the frontal sinus, respectively. All three forms are characterized by high remittent fever. Cavernous sinus thrombosis of the superior longitudinal sinus produces papilledema, edema and engorgement of the scalp, monoplegia or paraplegia.

The cerebral manifestations of *subacute bacterial endocarditis* and their distinction from those of the acute variety have already been mentioned. *Acute necrotizing hemorrhagic encephalopathy* is the term applied to a relatively rare disorder which occurs on a background of mild respiratory symptoms and is thought by some to represent a hypersensitivity state. It is characterized by fever, headache, stiff neck and the rapid evolution of crude focal neurological signs, stupor and coma. The spinal fluid contains many polymorphonuclear leukocytes and red cells, but the sugar content is not lowered. Pathologically, one sees a large asymmetrical discolored lesion, which consists of a widespread necrosis of tissue, including the blood vessels. The fulminant clinical course of this disorder, the eventual bilaterality of the neurological signs, the lack of an obvious source of infection and, as a rule, the spinal fluid findings help to distinguish it from cerebral abscess.

Rare instances of indolent and well encapsulated abscesses, which may run an afebrile course and excite only a few lymphocytes and modest elevation of protein in the spinal fluid, may be very difficult to distinguish from *neoplasm*. In fact, most neurosurgeons have had the experience of resecting what they thought was a neoplasm, only to discover an abscess. Occasionally, occlusion of a major cerebral artery and *massive infarction* of brain tissue may cause swelling of the hemisphere and an outpouring of neutrophils in the spinal fluid; the distinction from brain abscess should not be difficult.

THE MANAGEMENT OF BRAIN ABSCESS

The presence or absence of brain abscess is ultimately determined by exploring the brain with a ventricular needle, through a burr hole or small craniotomy. This procedure not only confirms the diagnosis but

represents the first step in treatment. In patients who are seriously ill and deteriorating rapidly, the more refined diagnostic measures such as arteriography and air studies may be dispensed with, and aspiration carried out on the basis of clinical localization alone.

If a septic focus is discovered, Thorotrast and a mixture of broad-spectrum antibiotics are injected into the area after the pus is aspirated. Cultures of the pus are made to determine the appropriate antibiotic treatment. X-ray films are then taken to determine the size and position of the lesion.

Two principal methods are used in the subsequent neurosurgical management of the abscess: one consists of repeated aspiration of the septic focus, and the other utilizes initial aspiration followed by total excision of the septic area. These methods are not mutually exclusive, and in most patients both aspiration and excision are employed. Repeated aspiration is the treatment of choice if the abscess is deeply located, poorly encapsulated or located in a strategic motor or speech area. In a relatively small number of patients this procedure alone succeeds in obliterating the abscess, as judged by successive films of the Thorotrast-outlined cavity. Pennybaker¹⁶ has reported 10 such patients in a series of 70 survivors. However, before accepting such patients as cured, they must be free of symptoms and signs, the Thorotrast-encrusted cavity must be shriveled up, the spinal fluid should be clear, and ventriculography should disclose no abnormalities.

Most surgeons are reluctant to depend on the effects of aspiration alone, since abscesses frequently have multiple noncommunicating loculi, only one of which is being tapped and visualized by Thorotrast. In fact, while one abscess cavity is healing, another may be ripening for rupture. Therefore, repeated aspiration, supplemented by the liberal use of local and general antibiotic therapy, are employed, with the purpose of tiding the abscess over to a chronic state, at which time total elective excision can be carried out. If the patient's condition permits, this is the method generally favored, since the excision of a well-encapsulated abscess is far less damaging to the brain tissue than the wide excision of a poorly demarcated area of suppuration.

On other occasions, however, aspiration alone fails to improve the clinical state, or to halt the progressively deteriorating course. If the patient's life is threatened by deepening coma, incipient rupture of the abscess into the ventricle and increasing intracranial pressure, the surgeon may be forced into immediate excision of the septic area, despite the increased hazards of operating under such circumstances.

It can be seen from even this brief review that the surgical treatment of brain abscess is a difficult and complex problem, and one that cannot be standardized for all patients. It is not important, from the practitioner's point of view, to be conversant with all the controversial details of surgical management. It is important to reiterate that early recognition is the key to effective management. One must therefore develop an awareness of the circumstances in which brain abscesses form, of the signs that indicate the infection has invaded the brain, and of the speed of evolution and unpredictability of the clinical course in many patients. It is advisable, as soon as the presence of intracranial suppuration is suspect, to call for the help of a neurologist experienced in this category of

disease. From that point onward, neurologist and neurosurgeon must work closely together in choosing the appropriate diagnostic measures and the moment of surgical intervention.

ILLUSTRATIVE CASES

The following brief case reports are intended to highlight certain clinical and pathological features of brain abscess and to illustrate some of the difficulties in diagnosis and management.

CASE I. An 8 year old boy was admitted to another hospital with otitis media and mastoiditis, fever, nausea and vomiting. Antibiotics were administered for 1 week and he was discharged. One month later there was an abrupt onset of headache, associated with vomiting and diplopia. He was readmitted to the hospital, where daily elevations of temperature to 101° F. were noted. He complained of diplopia and pain in the neck and became progressively more lethargic. Only after 10 days was the spinal fluid examined, disclosing 125 white cells (50 per cent neutrophils), protein 50 mg./100 ml., and a normal sugar. A few hours following this procedure he lapsed into coma. He reached our hospital in a respirator, where he died an hour later.

Necropsy disclosed a large cerebellar abscess (Fig. 1) from which alpha hemolytic streptococci were cultured. There was evidence of massive herniation of the cerebellar hemispheres through the foramen magnum.

Comment. The abrupt onset of headache signified the spread of infection from the middle ear to the intracranial structures. Investigative procedures should have been instituted at that time and not ten days later, at which time the intracranial pressure was very high and the lumbar puncture probably precipitated herniation of the cerebellum. The infection most likely reached the cerebellum via the veins; the location of the abscess and the tempo of the clinical course were quite characteristic.

CASE II. The patient was a 5 year old boy who began to complain of headaches 3 weeks before admission. The headaches became progressively more severe and were accompanied by anorexia and vomiting, and, shortly before admission, by increasing lethargy. He was known to have had a heart murmur from infancy, and since then he had progressive symptoms of myocardial insufficiency and intermittent cyanosis.

Initial examination disclosed an unresponsive child with a rigid neck, but no focal neurologic signs. There was a harsh systolic murmur and thrill along the left parasternal border. The spinal fluid was under a pressure of 270 mm. H₂O and contained 10,800 white blood cells, practically all neutrophils; no organisms were seen on smear or culture but the sugar content was greatly reduced. Blood cultures also showed no growth. The white blood count was 17,600 with a marked shift to the left. He was treated with broad-spectrum antibiotics.

Ventriculography was thought to show a shift of the fourth ventricle and aqueduct to the right and for this reason the cerebellum was tapped, with negative results. Later the left pupil became dilated, and the temporal and parietal lobes were needled, again without results. The intracranial pressure continued to rise, the patient became decerebrate, both pupils dilated, and he died 10 days after admission.

Postmortem examination revealed the characteristic cardiac anomalies of the

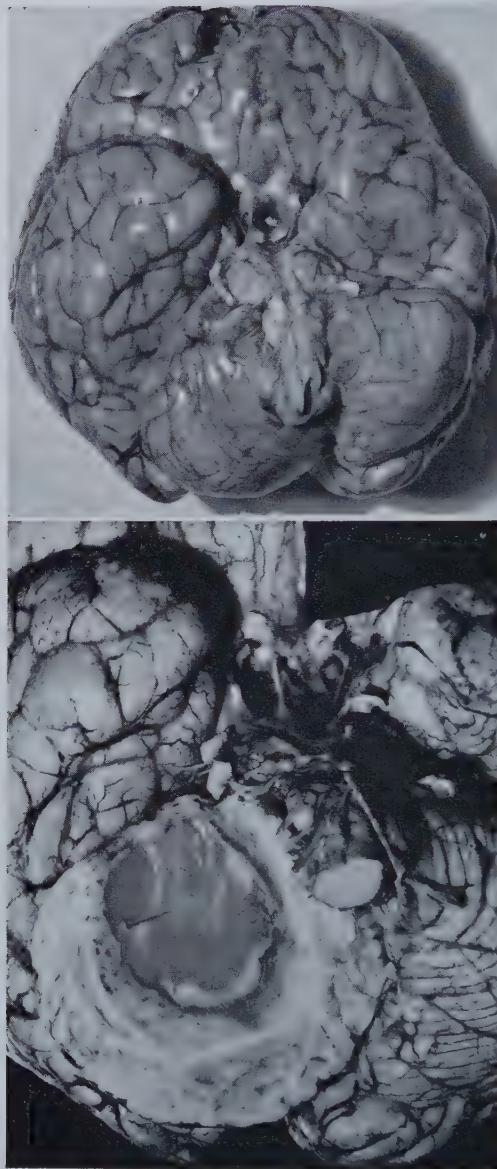


Fig. 1 (Case I). *Above:* Brain after fixation, demonstrating a swollen right cerebellar hemisphere with marked compression of the medulla by herniated cerebellar tissue. *Below:* A horizontal section through the right cerebellar hemisphere showing early incomplete capsule formation at the medial margin of the abscess.

tetralogy of Fallot. There was a healing meningitis and a solitary left thalamic abscess, which is illustrated in Figure 2. Samples from both the meninges and the abscess were sterile.

Comment. This case exemplifies the common association of congenital heart disease, particularly the tetralogy of Fallot, and a solitary brain abscess. The primary source of infection was not discovered, but it was probably responsible for both the abscess and the meningitis. The air



Fig. 2 (Case II). A solitary, encapsulated, subependymal abscess is seen in the left thalamus, distorting the lateral ventricle.

study was imperfect and failed to show a large thalamic abscess. Arteriography, which may have shown the lesion, was unfortunately not performed.

CASE III. Six days before admission this 29 year old man had the onset of severe occipital headaches, which soon became generalized and constant. These were followed in rapid succession by fever, nuchal rigidity, vomiting and lethargy and coma. Four months before his final admission, he was hospitalized with high fever, vomiting, abdominal pain, mild jaundice and tenderness of the liver. These symptoms improved, but 1 month later he again had fever and chills, this time with right-sided chest pain. Again, he seemingly recovered from these symptoms before the present illness began.

Examination on admission showed a fever of 102° F., marked nuchal rigidity, blurred optic discs, convulsive movements and probably paralysis of the right hand and arm. He was in deep coma. The spinal fluid was under a pressure of 390 mm. H₂O and contained 320,000 white cells, almost all polymorphonuclears. The sugar content was 15 mg./100 ml. and in subsequent examinations rose to 36 mg./100 ml.; the protein ranged from 700 to 1500 mg./100 ml. Chest films showed infiltration of the middle lobe with rounded radiolucent areas; this was interpreted as a staphylococcal pneumonia with abscess formation. Despite treatment with chloramphenicol, sulfisoxazole and erythromycin the patient never recovered consciousness and the fever continued. On the sixth day he developed supraventricular tachycardia and died shortly thereafter.

Autopsy showed focal healing liver abscesses, multiple abscesses of the middle lobe of the right lung and multiple brain abscesses, one of which had ruptured into the right ventricle. These lesions are illustrated in Figure 3. There was also a widespread ventriculitis and meningitis. A nonhemolytic *Staphylococcus albus*, coagulase-positive, was cultured from all the abscess sites.

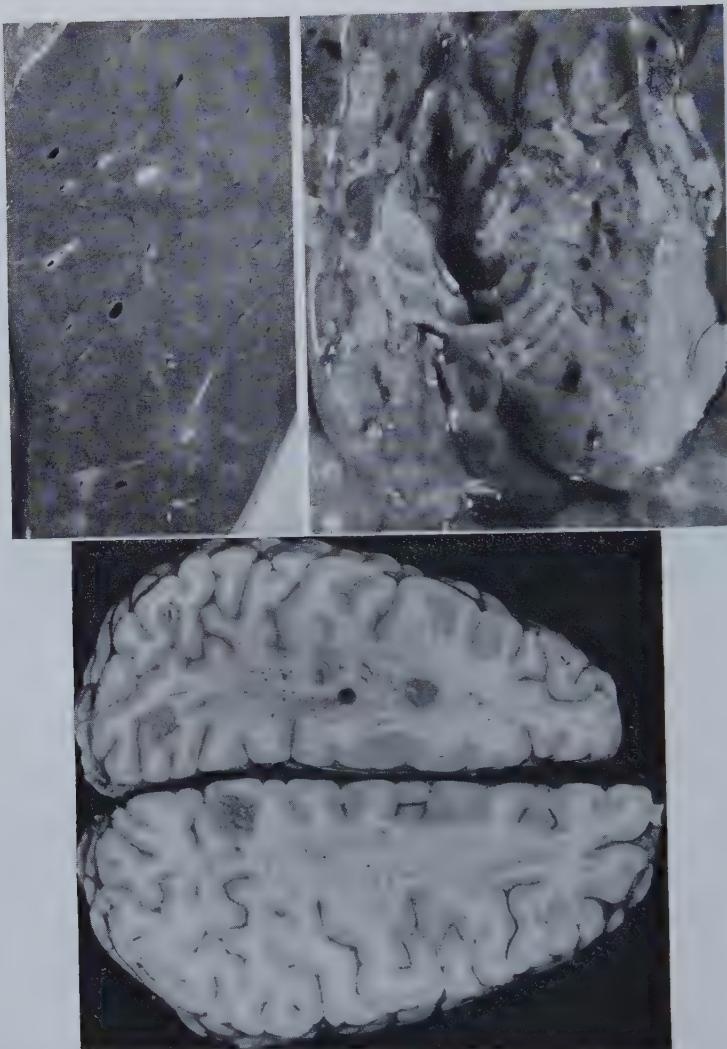


Fig. 3 (Case III). There are healing abscesses in the liver (*above, left*) and in the lung (*above, right*) and small metastatic abscesses in both cerebral hemispheres (*below*).

Comment. The sequence of clinical events involving liver, lungs and brain are readily explained by the pathological findings. The meningitis and the inordinately high white cell count in the spinal fluid were the result of rupture of an abscess into the ventricle. This case also emphasizes the differences between abscesses in the brain and other parts of the body. Whereas the abscesses in the liver had healed, and those in the lung were partially healed and well tolerated, the nervous parenchyma proved very vulnerable, offering virtually no defense against the fulminant spread of the infectious process.

CASE IV. A 12 year old girl was admitted to the hospital with a history of left-sided headache, nausea, vomiting and somnolence of 2 weeks' duration. Three days before admission the symptoms became much worse and she was intermittently confused. She was known to have had a chronic mastoiditis, and three mastoidectomies had been performed in the past, but these had failed to control the intermittent drainage from her left ear.

Examination disclosed a flushed, drowsy, young girl who responded slowly and somewhat inaccurately and complained of left frontal headache. Temperature ranged from 98 to 100° F. There was a mild right facial weakness and a question-



Fig. 4 (Case IV). *Above*, The left temporal lobe is swollen and the uncal portion had herniated through the tentorial opening. Thickened, adherent dura marks the abscess tract. *Below*, Coronal section of the brain disclosed a large encapsulated abscess in the left temporal lobe; the left lateral ventricle is compressed and shifted to the right.

able Babinski sign on that side. The spinal fluid was under a pressure of 290 mm. H₂O and contained one granulocyte and five lymphocytes. The protein content was 73 mg./100 ml. and the sugar was normal. The electroencephalogram showed diffuse slow activity, most pronounced in the left posterior temporal region. She died a few hours after ventriculography was performed.

At autopsy the meninges over the petrous portion of the left temporal bone region were thickened, discolored and adherent to the contiguous brain tissue. A well-encapsulated abscess of the temporal lobe was found in relation to the thickened meninges (Fig. 4).

Comment. This is an example of temporal lobe abscess that spread from an infected middle ear by direct extension. The investigation and treatment should have begun two weeks before her admission to the hospital, when the symptoms clearly indicated that the infection had spread intracranially.

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Recognition, Prognosis and Treatment of the Guillain-Barré Syndrome (Acute Idiopathic Polyneuritis)

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THE GUILLAIN-BARRÉ SYNDROME is an eponymous designation for acute or subacute polyneuritis of unknown etiology. The failure to identify a specific etiologic agent or to elucidate the pathophysiologic mechanism probably accounts for the considerable disagreement among authorities regarding the limits defining this disorder.^{1, 9, 12, 24, 30} Early publications describing a few cases failed to establish the wide spectrum of peripheral neurologic dysfunction which may occur.^{10, 16}

Although the symptoms and signs are of peripheral nerve disease, autopsy studies occasionally demonstrate inflammatory and demyelinating areas in the central nervous system as well as in the peripheral nerve. The lesions described closely resemble the changes observed in experimental animals sensitized to homologous nervous tissue.^{15, 32} The neuropathologic resemblance to these experimental states and the demonstration of complement fixing antibodies to nervous tissue in patients with Guillain-Barré syndrome¹⁸ suggests the disease is a hypersensitivity reaction. The nature of this hypersensitivity has not been established; however, the disease is often associated with a recent and relatively nonspecific illness which may have triggered an allergic process.

RECOGNITION

To emphasize the clinical features of acute polyneuritis of unknown cause, we have reviewed 48 patients referred for management to Cleve-

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Fig. 1. Age distribution of patients with Guillain-Barré syndrome (range 16 months to 62 years). C.M.G.H., 1946-1960. Black areas indicate distribution of fatal cases.

land Metropolitan General Hospital (City Hospital) between 1946 and 1960. Two-thirds of these cases were admitted in the last five years of the period reviewed, suggesting that the disease is increasing in frequency. A similar observation has been made by others.¹⁷ No seasonal variation has been noted.

All ages appear to be equally susceptible to the Guillain-Barré syndrome (Fig. 1). The distribution demonstrated is consistent with age distribution in the community as determined in the 1960 census.¹¹ The disease affects males more often than females: there was a 56 per cent male incidence in our series and a 3:2 male to female frequency in 174 cases in the literature,^{2, 6, 17, 19, 20, 22, 23, 24, 28, 31} excluding the Armed Forces Institute experience.¹²

Four (8 per cent) of the patients were Negro, a figure in keeping with percentage of Negroes in the population served by the hospital. This experience and others^{1, 17} is at variance with the previously suggested lower susceptibility in Negroes.¹²

Except for the occurrence of a nonspecific illness preceding the onset of symptoms of Guillain-Barré syndrome, there are no consistent predisposing factors apparent. Two of our patients and two of those of the Armed Forces Institute¹² were chronic alcoholics. There was no clear relationship to recent immunization in children. Acute illnesses occurring within 16 days of the onset of symptoms were reported in 25 (52 per cent) of our cases. Fifteen had upper respiratory infections and 13 had gastrointestinal symptoms or both. Overlapping of the nonspecific illness and the onset of polyneuritic symptoms was frequently observed.

Specific entities associated with Guillain-Barré syndrome in our series were rubella, rubeola, atypical pneumonia and infectious mononucleosis. Atypical pneumonia and infectious mononucleosis have been reported in association with this disease by others.^{2, 6, 12}

The earliest symptoms of the disease were sensory or motor disturbances in the extremities. Paresthesias, numbness or pain were described by 40 (83 per cent) of the patients. Muscle weakness was noted first by eight (17 per cent). Back pain was reported by four individuals, and sensory and motor dysfunction in cranial nerve distribution was the first indication of illness in two individuals.

Earliest muscle weakness noted was in the lower extremities in 22 and in upper extremities in seven. In 13 cases, the onset of weakness was so rapid that two or more areas appeared to become involved simultaneously; all four extremities were paralyzed suddenly in six subjects and limb, trunk and cranial nerves in seven. Muscle weakness often occurred abruptly while a patient was physically active; other individuals awakened from sleep with profound paresis.¹² The most severe muscle involvement tended to be proximal in distribution in contradistinction to the sensory symptoms which were largely distal. Oculomotor and facial weakness was seen as the earliest evidence of motor impairment in four cases.

Ataxia was noted out of proportion to the degree of muscle impairment in three of our cases.

Headache was reported by ten (23 per cent) of the patients. However, sensorium was invariably clear.

PROGRESSION OF SYMPTOMS

Progressive weakness characterizes the Guillain-Barré syndrome while sensory changes are not invariable. Since sensory testing represents the most exacting part of the neurological examination, it is evident that sensory assessment might not correlate well with the more readily detectable motor impairment. In general, hypalgesia, hypesthesia and hyperpathia were frequently (31 [70 per cent] of the patients in our series) noted, particularly in distal distribution in both upper and lower extremities, most frequently the latter. Impaired position and vibratory sensibility were common, particularly when ataxia was a major presenting sign.

Progression of weakness is diagrammatically represented in Figure 2. The pattern of muscle impairment was variable in axial distribution but fairly consistently symmetrical. Muscle pain and tenderness was observed in approximately half of the cases. Tendon stretch responses were diminished or absent in areas of involvement, and superficial reflexes were reduced or absent in a majority of cases. Fasciculations were infrequently observed, and atrophy was ordinarily not profound.

In our series cranial nerve involvement occurred in 35 cases (76 per cent) (Table 1); 28 exhibited multiple involvement; six showed facial involvement alone; and one had isolated involvement of oculomotor nerves. Diplegia was observed in 20 of 2 cases with facial paresis, and 24 patients had impaired swallowing function.

Respiratory impairment severe enough to require support of respiration in the tank respirator occurred in 21 patients (44 per cent). This apparent high frequency of severely involved cases may have been by selection since the hospital serves as a regional respiratory care center.

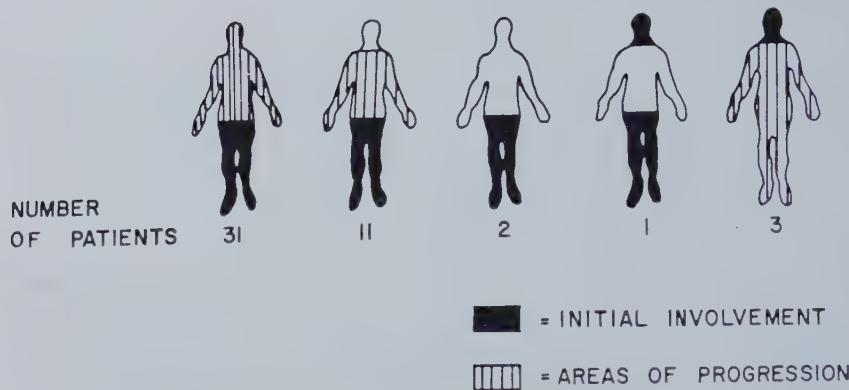


Fig. 2. Distribution of initial motor impairment and pattern of progression in 48 cases of Guillain-Barré syndrome.

The clinical course was more rapidly progressive in the patients who developed respiratory failure (Fig. 3). The mean difference of the duration of progression of paresis between patients with respiratory paralysis and those without respiratory involvement is highly significant. Severe respiratory insufficiency was almost invariably complicated by involvement of bulbar musculature.

Fever is not characteristic of acute polyneuritis: 18 of our cases had fever, but this was due to complicating infection in all but four. Urinary incontinence or retention was observed transiently in about 25 per cent of our cases, and fecal incontinence in two individuals.

The occurrence of hypertension in patients with Guillain-Barré syndrome has not been emphasized in previous writings but was an impressive feature of this illness in our experience. Diastolic pressures in excess of 90 mm. Hg in adults and 15 mm. Hg above normal in children were observed in 29 (60 per cent) of the cases reviewed. Blood pressure measurements were recorded at least four times daily in 39 cases; 20 of these patients had respiratory failure and 19 did not. The difference in occurrence of hypertension in the patients with respiratory insufficiency (95 per cent) and those without (53 per cent) is highly significant.

Table 1. Frequency and Distribution of Cranial Nerve Involvement in 48 Patients with the Guillain-Barré Syndrome

LOCATION	CASES	
	Number	Per cent
Cranial Nerves	35	76
III, IV, VI	5	11
V	8	17
VII	28	61
IX, X	24	52
XI	10	22
XII	3	7

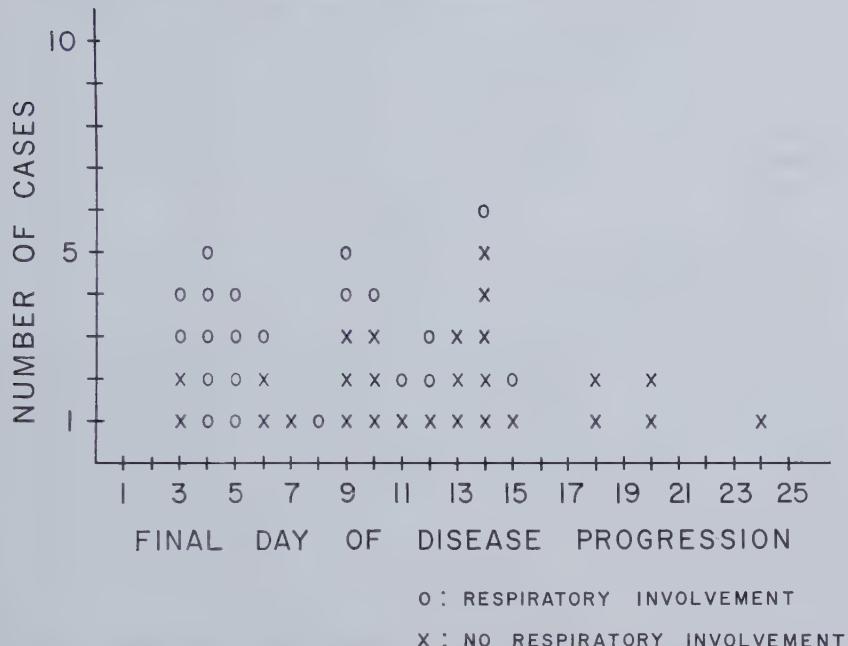


Fig. 3. Duration from onset to cessation of progression of motor impairment in 48 patients with Guillain-Barré syndrome.

That hypertension in these patients represents a disturbance in neural control and correlates best with severity of involvement is supported by the observed occurrence in patients without respiratory paralysis and the fact that hypertension was noted one to four days before the development of respiratory muscle involvement in seven cases.

In general, hypertension was a transient phenomenon noted at the height of the illness. A few patients, however, ran persistently elevated pressures for over three months.

A remarkably labile blood pressure was a bad prognostic sign, being reported in five cases all terminating fatally.

Nuchal rigidity was observed in approximately one-third of our cases.

LABORATORY FINDINGS

Peripheral blood studies revealed no characteristic pattern in this condition. The hemoglobin and red and white cell counts were normal unless the picture was complicated by infection. Differential smears revealed no specific abnormality with the exception of atypical lymphocytes accompanying infectious mononucleosis.

Urinalysis and blood chemical values were normal in the uncomplicated case.

Serologic studies were useful only in confirming the nature of the antecedent illness. High cold agglutinin titers were observed in the single case recognized to have atypical pneumonia and were normal in 5 cases. Elevated heterophile antibody titers were observed in the case with infectious mononucleosis and not in 18 others studied.

Bacteriological studies of blood and spinal fluid were negative. Pharyngeal cultures were positive for Group A beta hemolytic streptococci in 3 instances but otherwise revealed nonspecific and variable flora.

Virological studies on CSF specimens in 14 cases were negative. ECHO 6 enterovirus was recovered from feces in a fatal case but could not be isolated from brain, blood, or spinal cord. Coxsackie strain A₉ was isolated from feces in another case. A clear etiological relationship between these viruses and the syndrome is not established although others have also isolated viruses from polyneuropathy cases.²⁵

Cerebrospinal fluid examination revealed opening pressures elevated to 200-300 mm. of CSF in 10 of 48 patients. Papilledema was not observed but has been reported.^{1, 12, 17} Pleocytosis of less than 10 cells per mm.³ was observed in 42 patients. The highest cell count recorded was 70. In all instances, mononuclear cells predominated, polymorphonuclear cells did not exceed 6 per mm.³

Elevation of spinal fluid protein was observed in 40 of 48 cases at the time of admission, and a subsequent rise to abnormal levels was documented in 7 more. Levels ranged from 40-900 mg./100 ml., but there was no apparent correlation between protein level and clinical course and the protein continued to rise as some patients improved clinically. (Levels may begin to fall in 1 to 6 weeks.) Persistently high levels were noted as long as 71 days after onset of illness, the earliest observed return to completely normal levels was approximately 60 days after onset.

DIFFERENTIAL DIAGNOSIS

The diverse character of symptoms of acute polyneuropathy poses a challenge in early diagnosis. Conditions that must be differentiated are poliomyelitis, postinfectious encephalomyelitis, epidural abscess, acute porphyria, postdiphtheritic paralysis, carcinomatous polyneuropathy, alcoholic nutritional polyneuritis, Wernicke's disease and hysteria. Some major points in differentiating these conditions follow.^{1, 14}

Poliomyelitis has a febrile course, an absence of sensory findings, and an irregular distribution and severity of muscle involvement. Meningeal signs are usually present and a definite seasonal pattern is usually observed. Significant pleocytosis with relatively mild protein elevations is almost invariably found.

In *postinfectious encephalomyelitis* an alteration in sensorium is frequently observed, the course is often febrile, and convulsions may occur. Spinal sensory levels involving trunk and long tract signs (extensor plantar reflexes) are characteristic. Early and severe bladder and bowel dysfunction is quite common.

In *epidural abscess* fever, pain and leukocytosis with percussion tenderness over the spine and demonstration of a spinal fluid block are the most striking differential features.

Acute porphyria is suggested by psychic aberration, abdominal pain, and progressive muscle impairment and the diagnosis may be substantiated by definite family history and the demonstration of porphobilinogen in the urine.

Oculomotor palsy, blurred vision, delayed and relatively slow development of sensory-motor involvement of the extremities are observed in *postdiphtheritic paralysis*. This diagnosis may be suspected with the demonstration of myocarditis and confirmed by culture of the bacillus from the patient or contacts.

Usually demonstrating a subacute course of polyneuritis, the diagnosis of *carcinomatous polyneuropathy* requires the demonstration of coexisting malignancy.

Alcoholic Nutritional Polyneuritis. The history and poor nutritional state

of the patient, skin changes, burning paresthesias of the feet, and normal spinal fluid protein are most helpful differential features of this disorder. Postural hypotension, ophthalmoparesis and nystagmus in addition are observed in Wernicke's disease.

Hysteria. Anatomically and physiologically inconsistent motor and sensory changes, elucidation of gain from illness, and a normal CSF examination suggest this diagnosis.

PROGNOSIS

The mortality in the Guillain-Barré syndrome is reported to be from 0¹³ to 40 per cent.^{1, 14} In our series, nine cases (19 per cent) terminated fatally. Death may be abrupt, unexpected and inadequately explained at postmortem examination. Sudden deaths have occurred during tracheal aspiration presumably from reflex cardiac arrest. Errors in management clearly contributed to the observed mortality. Inadequate support of respiration through ill advised use of the lesser respiratory aids or incorrect setting of tank respirator pressures certainly contributed to the significant mortality.

Atelectasis, pneumonitis and pulmonary abscesses were considered the major reasons for fatal outcome in six cases.

Myocarditis was found in one case and has been noted by others.³¹ However, it is unlikely that this condition contributes significantly to the disease mortality.

Survivors, in our experience, begin to show evidence of return of function two days to two weeks after the cessation of progression. However, one individual showed no change for over a month. Rate of recovery was remarkably variable but was unassociated with relapses which others have described.¹ In quadriparetics, recovery tended to occur in descending pattern, the last detectable motor involvement lingering in the lower extremities of 19 patients. Functional levels of motor power were attained within four months in the majority of cases. Although most cases are ambulatory and essentially independent within a year, slow gains have been observed to occur over an 18 month period in a few.

TREATMENT

The obscure etiology of Guillain-Barré syndrome limits the clinician to applying supportive measures in managing patients. The most critical considerations in the individual case are the recognition and management, respectively, of airway obstruction, respiratory insufficiency and peripheral vascular collapse.

Isolated severe pharyngeal and/or laryngeal paralysis is rare in acute polyneuropathy. Pure bulbar paresis can be managed with careful positioning and suctioning. However, the combination of pharyngeal paralysis and respiratory muscle weakness requires tracheostomy. If possible, the procedure should be performed electively. An adequate airway is assured when an endotracheal tube is first inserted and ventilation is supported. When tracheostomy is performed as an emergency, hypoxia may considerably increase the risk of cardiac arrest from hyperactive vagal reflexes. Intravenous atropine (0.6 mg.) protects against

vagal induced cardiac arrhythmia and arrest from tracheal manipulation.

Although progression of muscular weakness may be rapid, there are several clues to impending respiratory failure. Restlessness, sleeplessness and apprehension are common early manifestations. These signs may be manifested without subjective breathlessness and without great alteration in respiratory rate and depth. Development of significant arm and shoulder weakness frequently precedes diaphragmatic paresis and may signal impending respiratory insufficiency.

Serial vital capacity measurements are very useful in gauging the severity of respiratory failure. Usually, pre-illness measurements of vital capacity are not available; they may be estimated and compared with measured values as a guide to the need for artificial respiration. Vital capacity in children is roughly 200 cc. per year of age. Adult male vital capacity is approximately 25 cc. per cm. of height, and in the female approximately 20 cc. per cm. of height.

If vital capacity falls to approximately 50 per cent of predicted normal, it is wise to begin brief trial periods in the tank respirator, for in time the patient is certain to tire and need prolonged respiratory assistance. If the patient's initial introduction to the body respirator is not entirely successful, he is less overwhelmed and can gain a measure of reassurance in the fact that he can be taken out of the machine. It cannot be overemphasized how fearful patients are of the "iron lung" and appropriate management demands a sympathetic, confident and competent staff.

If vital capacity falls to 30 per cent of predicted normal, respiratory support is mandatory. Intra-tank pressures for adequate ventilation vary with individuals. Pressures between 15 and 20 cm. of water negative pressure are usually required for children and adults. Repeated tidal ventilation measurement while the patient is in the tank with pressure adjustments made to provide levels appropriate for body size as determined by a nomogram²⁸ is the only method to assure adequate ventilation.

Frequent positioning and movement and attention to the patient's comfort are essential. The patient who does not have a tracheotomy may be turned completely onto his abdomen in the tank to insure expansion of all lung segments.

The patient with progressing disease and swallowing paralysis should be tracheostomized. The largest tube that can be accommodated is preferred. Tracheal aspiration should be carefully performed and the method described by Plum²⁷ is recommended.

Pulse, respiration and blood pressure should be monitored closely. Falling blood pressure may require support with Neo-Synephrine or norepinephrine. Shock is exaggerated by the tank respirator. The effect may be minimized by providing 5 to 7 cm. of water positive pressure during the expiratory phase of respiration.

Fluid balance must be maintained, if necessary intravenously. Alimentation in patients with severe bulbar involvement may be instituted after a few days by indwelling plastic nasogastric tube. Low calcium intake may be achieved by feeding the patient an osterized low calcium diet rather than the traditional milk-base tube feedings.

With recovery, withdrawal from respiratory support should be gradual and guided by vital capacity measurements. Following profound respiratory failure, patients regaining 20 to 25 per cent of predicted vital capacity may tolerate short periods without respiratory support and attain freedom when levels of 35 to 40 per cent are again achieved. During recovery, the rocking bed and cuirass respirators are of considerable value in the management of the patient. Again, adequacy of ventilation cannot be guessed and must be measured. In general, small children are not adequately ventilated on the rocking bed.

Proper positioning, range of motion exercises and, when the patient's condition permits, a more vigorous physical therapy program should follow in orderly sequence.

Steroids

As has been true with many conditions of obscure etiology, steroids were employed empirically in the treatment of Guillain-Barré syndrome.^{3, 4, 5, 6, 14, 21, 23, 26, 31} With the demonstration of characteristic findings of Guillain-Barré syndrome in "allergic neuritis" in the experimental animal,³² steroid therapy became much more widely accepted in view of its recognized application in hypersensitivity states.^{2, 7, 8, 13} Conclusive evidence that steroid therapy significantly alters the course of the disease, however, is still unavailable.¹³

Impressed by the problem of infection complicating the management of respiratory failure and disturbed by the unpredictable and at times disastrous consequences of steroid therapy in bacterial and viral infections, we have refrained from their use in the management of the Guillain-Barré syndrome.

SUMMARY

In Guillain-Barré syndrome one characteristically sees the development of muscle weakness following closely upon a relatively nonspecific illness. There are frequently associated mild sensory symptoms of feet and hands. Early in the illness, examination may be remarkably unrevealing. However, progression leading to profound impairment of extremity, trunk and bulbar musculature may follow in a relatively short period of time. Except for a fairly consistent cerebrospinal fluid picture of albuminocytologic dissociation, laboratory studies are nondiagnostic.

Until therapy can eventually be directed against a specific etiologic agent, the important consideration remains the identification and appropriate management of respiratory insufficiency.

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The Diagnosis and Management of Parasitic Diseases

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PARASITIC DISEASES are due to infestation with protozoa or helminths. The helminths consist of flukes (trematodes), tapeworms (cestodes) and round worms (nematodes). Over 100 parasites may infest the human being but only around 50 of these are potentially harmful to man.

The incidence of parasitic diseases in the United States is not accurately known as a significant number of infested people may be asymptomatic or suffering from mild symptoms which do not prompt them to look for medical advice. On other occasions the examining physician might overlook an investigation for parasites in patients with mild nonspecific symptoms.

The diagnosis of parasitic disease depends to a large extent upon an initial high index of clinical suspicion followed by carefully performed laboratory examinations by an experienced technologist on adequately collected samples. Although serological tests are helpful in establishing the diagnosis, it is the isolation of the organisms, their larvae or their ova that actually clinches the diagnosis. Most of the tests consist of the examination of specimens of blood and feces. Examination of the sputum, bone marrow, cerebrospinal fluid and tissues is required for diagnosis in some specific parasitic infections.

Although there has been considerable progress in the understanding and management of parasitic diseases, we still face some that cannot be controlled with our most refined therapeutic agents.

Because of limitations of space we will limit this presentation to ten of the most frequently encountered parasitic diseases.

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PROTOZOAL INFECTIONS**Amebiasis**

This illness is due to infestation with the protozoa *Entamoeba histolytica* which is acquired by the ingestion of cysts by the human being. The patient might be asymptomatic (carriers) or develop an acute or chronic dysenteric type of picture. Sometimes encountered is an enteritis, a granuloma (ameboma), a liver abscess or abscesses in distant tissues such as the lungs and brain.

It is estimated that there is a carrier incidence of 8 to 10 per cent in the United States. In the diagnosis of intestinal amebiasis with colonic changes sigmoidoscopic examination is very helpful, revealing typical ulcerations with normal intervening mucosa. The entamoebae are most frequently found in mushy rather than in formed stools. It is important to examine the warm stools as soon as possible and not later than 30 minutes after the fecal specimen is taken in order to identify the living trophozoite. The trophozoites of *E. histolytica* have a well defined broad ectoplasm and show ingested erythrocytes, active motility and finger-like pseudopods. When there is no diarrhea the use of laxatives may be helpful in increasing the opportunities of obtaining cysts. The stool specimen may be examined as a wet unstained smear prepared with normal saline or as wet smears stained by Lugol's solution or eosin.

The stool has an offensive odor, is acid in character and when accompanied by blood and mucus is more suggestive of the disease. A single negative fecal examination does not exclude amebic dysentery or enteritis. Negative fecal examinations are frequently encountered in amebic hepatitis or hepatic abscess. Dramatic response to antiamebic therapy is helpful in the diagnosis of hepatic involvement. Characteristically there is no eosinophilia in amebiasis. The complement fixation test is not very helpful.

The management of amebiasis is somewhat dependent upon the localization of the disease in the intestines or in the liver.

For the intestinal phase paronomycin, tetracycline, oxytetracycline, fumagillin, erythromycin, diiodohydroxyquin (Diodoquin) and arsenicals such as carbarsone or glycobarsol (Milibis) may be used.

Paronomycin (Humatin) is given in doses of 500 mg. three times a day for a period of five days in the adult;³ in children, 10 mg. per pound of body weight per day for the same period. Milibis is given in doses of 500 mg. three times a day for eight days, Diodoquin in doses of 25 to 30 mg. per kilogram of body weight daily for 15 to 20 days.

A recent amebicide, entamide furoate (Furamide), has been claimed to be useful in acute amebic dysentery and chronic amebic colitis in doses of 500 mg. three times a day for ten days.²¹ Corroboration of this finding with a larger series of patients is still needed.

It is the general impression that for the hepatic disease an emetine derivative such as emetine hydrochloride and a 4 amino-quinoline such as chloroquine are needed. Emetine hydrochloride is given by deep subcutaneous injection in a daily adult dose not greater than 1 mg. per kilogram of body weight and not surpassing a daily dose of 65 mg. for a period of five to ten days. Chloroquine is given in the adult as 1 gm.

daily for two days and 0.5 gm. daily thereafter for ten days. Aspiration might be required in hepatic abscess.

Dehydroemetine, a new synthetic compound, has also been used successfully in hepatic amebiasis in doses of 80 mg. intramuscularly daily for ten days followed by an interval of 14 days and then by a second similar course for six days.¹⁸ Concurrently diiodohydroxyquino-line is administered in doses of 600 mg. three times daily for 20 days.

NEMATODE INFECTIONS

Ascariasis

Ascariasis is most frequently encountered in children and young adults. Clinical symptoms may be absent or vague. During the migration of the larvae pulmonary wheezing and eosinophilia may be encountered. Severe infections may be accompanied by complications such as intestinal obstruction and perforation of the intestines. These complications are frequently associated with the administration of diethylcarbamazine (Hetrazan), so the use of this drug is contraindicated.

The presence of the infection is usually recognized when the round worm is discharged in the feces or occasionally in vomitus. A significant number of cases is diagnosed by the identification of the ova in a routine microscopic examination of the stool. Concentrated stool specimens may facilitate the diagnosis. Occasionally a barium contrast x-ray of the intestinal tract will reveal the presence of the worms or a wandering larva may be coughed up in the sputum.

Piperazine is the drug of choice.¹⁶ A dose of 70 mg. per pound of body weight without exceeding a total of 3 gm. to be repeated in a week is an acceptable therapeutic regimen. In massive infestations a dose of 30 mg. per pound per day may be used for a period of seven consecutive days. Neither fasting nor purgation is required.

Piperazine salts commonly used are the citrate, hexahydrate, adipate, phosphate and tartrate. The dosage is expressed according to the equivalence to piperazine hexahydrate. The medication is available as tablets, chewable wafers and syrups. Some of the trade names are Antepar, Bryrel, Nermidal, Pipizan and Vermizine.

Hexylresorcinol, dithiazanine and bephenium compounds are also effective.

Hookworm

Hookworm infection is prevalent through all tropical and subtropical countries and is one of the most important nematode diseases in humans. The two types which primordially affect man are *Ancylostoma duodenale* and *Necator americanus*, the latter being the predominant species in the New World.

The pathogenesis of clinical manifestations depends on the balance of two variables: the amount of blood loss and the ability of the human organism to compensate for such loss. The amount of blood loss depends directly on the number of worms present; the greater the number of feeding parasites the greater the loss. The second variable depends on the physiological mechanisms for compensation of blood loss, which to a

certain extent are dependent on the supply of dietary raw material. Thus the greater the worm load and the poorer the diet, the greater the chances for the development of clinical manifestations, which we characterize as hookworm disease. The basic clinical manifestations of hookworm disease are mainly due to hypoproteinemia and to ferropenic anemia.

The diagnosis is confirmed by the demonstration of the ova in the stools. A fresh sample should be examined to avoid the necessity of differentiating the rhabditiform larvae of hookworm and strongyloides. A quantitative determination of ova in the stools is desirable, either by the Stoll or Beaver methods, the latter being easier to perform. Occult blood in the stools may be present. The blood findings range from normal to marked eosinophilia and hypochromic microcytic anemia. In severe cases the serum iron is low and the serum iron clearance is accelerated. The serum albumin may be decreased to edema levels.

The treatment of the patient with hookworm infection is based on three premises: the correction of the anemia and malnutrition, eradication of the worm and the prevention of reinfection.

If anemia is severe with evidence of circulatory embarrassment, we give slowly 250 cc. of packed red cells every 12 to 24 hours until the level of hemoglobin is from 7 to 8 gm.

The patient should be started on a high caloric and high protein diet with oral or parenteral supplements of iron. Oral ferrous sulfate should be started in doses of 100 mg. t.i.d. and gradually increased to 0.33 gm. t.i.d. Parenteral iron, calculated according to the hemoglobin deficit, can be used. Hemoglobin levels increase more quickly with parenteral iron than with oral iron.

The drug of choice at present for the treatment of hookworm is tetrachloroethylene. It is a cheap, fairly safe drug which has been extensively used. Purgatives are not needed before or after the administration of the drug, unless one desires to recover and count the worms after treatment. Alcohol and fatty foods are avoided the evening prior to treatment. The drug is given in the morning with the patient fasting. The usual dose for adults is 5 ml. given in soft gelatin capsules; for children, it is approximately 0.66 mg. per pound of body weight. No food is given for four hours after treatment, after which a normal diet is allowed. Alcohol and highly fatty foods are prohibited for 24 hours after the treatment is given. An occasional side reaction is a mild dizziness which disappears spontaneously. Drowsiness, peculiar behavior and loss of coordination have been reported.

Bephenium hydroxynaphthoate has been used during the last years with a cure rate ranging from 30 to about 82 per cent and with significant decrease of worm load in the other cases.^{1, 10, 13, 24} Side reactions occur in about one-third of the patients, mainly nausea, vomiting, abdominal discomfort, diarrhea and dizziness. One schedule of treatment consists of administration of a 2.5 gm. dose in the morning for five to seven days. Farid and Miale⁷ report a 74 per cent cure rate in Egypt using a single dose of 2.5 gm. base given fasting in the morning. The authors point out that the drug seems to be more effective in *A. duodenale* than in *N. americanus* infections.

Strongyloidiasis

Strongyloides stercoralis is a parasitic infection occurring in the tropical and subtropical regions. The adult female parasite buries in the mucosa and submucosa of the human intestine. The adult males do not penetrate the mucosa and are eliminated soon after mating. Soon after oviposition the ova of *strongyloides* hatch into a rhabditiform larva in the intestine. The rhabditiform larva may develop into the filariform larva which is capable of infecting man. At times infective filariform larvae may develop in the lower intestine and penetrate the intestinal wall and/or perianal skin of the host, leading to severe autoinfections. But the rhabditiform larva passed in the stool, under favorable conditions, may also develop into free living adult parasites, capable of perpetuating the species in the soil and of producing filariform larva to infect man.

The infection through the skin and migration through the lungs may produce symptoms and signs similar to those of hookworm, but in many instances these stages are asymptomatic. If infections are mild, no intestinal symptoms appear. In massive infections, abdominal pain and severe bloody diarrhea may develop; intestinal perforation may occur and myriads of larvae may be found in the lungs and heart. Fortunately, these severe hyperinfections are rare.

The diagnosis is confirmed by finding the rhabditiform larva in the fresh stool. In stools which are not immediately examined it may be difficult to distinguish between rhabditiform larva of *strongyloides* and hookworm. The white blood count may reveal eosinophilia.

All patients with *strongyloides* should be treated to avoid spread of the disease and to prevent the possibility of self-infection which may lead to severe and even fatal disease. The drug of choice is dithiazanine. The usual treatment in adults is 100 mg. three times daily for 14 days. If the initial course of treatment is ineffective, two weeks after its termination the dose should be increased to 200 mg. t.i.d. and given for 14 days. For children weighing more than 20 pounds the usual dose is 50 mg. for every pound of body weight, given in three divided doses for 14 to 21 days. The daily dose should not exceed 300 mg.

Muhleisen reports 90 per cent cure with a similar treatment, except that he used 600 mg. during the first three days and the 300 mg. daily to complete 21 days of treatment.¹⁷ With an eight day treatment Guerrero found a 93 per cent cure rate.⁸

Enterobiasis

Enterobiasis (pinworm) is an intestinal infection due to *Enterobius vermicularis*. The infection is acquired by swallowing the ova. The ova develop into mature parasites which live in the colon attached to the mucosa. Two weeks after infection the female worm may be producing eggs, which are deposited in the perianal region by the migrating female. This may produce pruritus which is the clinical symptom of the disease. The problem with enterobiasis is that frequently the whole family becomes infected and usually the entire family should receive treatment. Unless personal hygienic measures and cleaning of the quarters are instituted concomitantly with anthelmintic therapy of the family, the infection cannot be eradicated.

The diagnosis may be confirmed by observing the worms in the perianal region early in the morning. The ova can be recovered from the perianal region with the aid of Scotch tape by firmly placing the sticky side over the perianal rugae. A tongue depressor or test tube is helpful in performing the procedure. The Scotch tape is fastened to a glass slide and observed under the microscope. If the patient has washed the perianal region just prior to the medical consultation, the ova are often not found. The ova may be demonstrated in the stool in 5 to 10 per cent of the patients.

Two excellent drugs with very few side reactions are available for treatment of the infected patient. Piperazine is used for seven days. Adults should receive 2 gm. daily and children under 60 pounds should get 250 mg. for every 15 pounds of body weight. A single morning dose is adequate. The drug is marketed in tablets of 250 mg., in syrups usually containing 100 mg. per ml., and in mint-flavored wafers containing 500 mg. of piperazine phosphate to facilitate administration to children. Pyrvinium pamoate is as effective as piperazine. It requires only a single administration in doses of 5 mg. per kilogram of body weight. The patient should be informed that it produces a red stain on the underwear.

Though effective, oxytetracycline should not be used for the treatment of pinworm as it is more expensive and occasionally it might sensitize the patient. The use of zinc oxide ointment applied to the rectum may be an adjuvant in treatment.¹²

Trichuriasis (Whipworm Infection)

Trichuris is a small round worm measuring 3 to 5 cm. in length which lives in the colon and cecum. There the worms produce ova which are passed in the stools. Man becomes infected by swallowing the embryonated eggs, from which a larva develops in the intestine. Trichuris is found in all warm, moist regions of the world.

Light infections are usually asymptomatic, the patient being treated only to prevent spread of the disease. Severe infections lead to a chronic, bloody diarrhea, hypochromic anemia, weight loss and severe malnutrition.

The diagnosis is usually made by the examination of the stool. The Beaver or Stoll egg count may give an idea of the severity of infection. In massive infection the sigmoidoscopic examination may show hundreds of worms attached to a friable, bleeding mucosa.

The drug of choice is dithiazanine. The usual treatment in adults is the administration of 200 mg. three times a day during five days. In children the dose is 100 mg. for every 10 pounds of body weight, taking the precaution of not exceeding the daily dose of 600 mg. Some prefer to use half doses during the first day of treatment to decrease side reaction. The course can be repeated in two weeks. In severe trichuris infections the treatment should be prolonged for 10 to 14 days.

Side reactions to dithiazanine occur in about 30 per cent of the cases, consisting mainly of abdominal cramps, anorexia, nausea, vomiting and diarrhea. They are more prominent during the first day of treatment. In many instances discontinuation of treatment is not warranted, but if severe nausea and vomiting develop the drug should be stopped.

Treatment should be postponed in acutely ill and dehydrated patients. The drug should not be administered in the presence of severe renal disease.

Swartzwelder and associates using 200 mg. of dithiazanine three times daily for five days reported a cure rate of 97 per cent.²² Guerrero and associates using daily doses of 200 mg. for persons weighing under 15 kg., 400 mg. for those weighing 16 to 30 kg. and 600 mg. for those weighing over 30 kg. and the drug being administered for eight days reported a cure rate of 67 per cent and a significant reduction of the egg count in the others. Mild side reactions occurred in 43.5 per cent of the cases.⁸ Albornoz-Plata, using the standard five day treatment, was successful in all cases. Mild side reactions were present in 44 per cent of the cases.² Studies in Borneo revealed an 80 per cent cure rate.⁶

Trichinosis

Trichinosis is caused by *Trichinella spiralis*. The diagnosis is suggested by the history of the recent ingestion of inadequately cooked pork products. This is followed in two to seven days by mild to severe non-specific symptoms of gastroenteritis such as nausea, vomiting, abdominal pain and diarrhea. About the second week after infection a new clinical picture develops. It is characterized by palpebral edema, fever which may be as high as 104° F., severe myalgias, subungual hemorrhages, nuchal rigidity and at times neurological deficits and myocarditis. Hypoproteinemia and edema are frequent. Usually there is a leukocytosis that might reach levels of 25,000 per cubic millimeter with a significant eosinophilia that might be as high as 40 per cent. The absence of eosinophilia in some instances conveys a poorer prognosis. The sedimentation rate is not elevated. The creatinine excretion in the urine per 24 hours might be significantly increased, occasionally reaching levels as high as 900 mg. per 24 hours. This is due to the damage suffered by the striated muscle where the parasite is predominantly localized.

The trichinella skin test with a 1:7000 or a 1:10,000 dilution of larvae antigen might give an immediate reaction in 15 to 25 minutes with a wheal and erythema or a delayed tuberculin type of reaction in 24 hours with a red papule. After the third week of infection, it is positive in 90 per cent of the cases. A positive skin test most likely proves that the patient has been infested with trichinella but it does not tell how recent was the patient's exposure to the parasite. Nonspecific positive reactions might occur when the patient has ingested meat containing nonviable trichinae.

The precipitin test becomes positive around the third week of disease and remains positive for a period of about a year. A positive precipitin test is more suggestive of a recent disease.

The larvae are occasionally identified by microscopic examination of blood laked by a 3 per cent acetic acid solution. The most reliable diagnostic procedure that we have at hand today is the identification of the organism by muscle biopsy. A single biopsy may be positive in about 50 per cent of the cases.

There is no specific treatment for trichinosis. Death follows in about 5 per cent of the clinically recognized cases of the disease. ACTH and

steroids have been helpful in controlling severe systemic reactions, apparently by their anti-inflammatory and antiallergic effects. Forty units of ACTH may be given intramuscularly two or three times daily for two or three days, then 40 units daily for one to two weeks, then 20 units daily until the fourth week of the disease.

Analgesics such as acetylsalicylic acid may be given every four hours for the relief of the myalgias. A good dietary intake should be provided. Bed rest is mandatory if myocarditis is present.

Larva Migrans

CUTANEOUS LARVA MIGRANS. This is known as "creeping eruption" and is caused by the filariform larvae of the dog and cat hookworm, usually *Ancylostoma brasiliense*. The larvae that develop from the eggs present in the dog feces penetrate the skin and during their migration produce irregular, easily identifiable, pruritic, erythematous, linear, serpiginous skin lesions. Eosinophilia is frequently encountered in the peripheral blood and there may be transitory patchy infiltrates of the lungs.

Local measures should be used to avoid concurrent bacterial infection. Ethyl chloride spray or carbon dioxide snow applied to the advancing area will control the disease in most instances. Local or intramuscular Fuadin, diethylcarbamazine and piperazine have been used with doubtful results.

VISCERAL LARVA MIGRANS. This occurs mainly in children who have ingested eggs of nematodes whose life cycle are completed in the dog and cat, i.e., *Toxocara canis* and *Toxocara mystax*. The disseminated larvae may cause fever, anorexia, myalgias, skin rash, hepatomegaly, pneumonitis, peripheral eosinophilia and hyperglobulinemia.

A hemagglutination test with ascaris and *Toxocara* antigens has been valuable in the diagnosis of the disease.¹⁴ Liver biopsy may reveal typical eosinophilic granulomatous lesions and larvae which will confirm the diagnosis.

There is no specific treatment but in patients with severe pulmonary findings ACTH may be helpful, apparently by its value in ameliorating hypersensitivity reactions.

CESTODE INFECTIONS

Tapeworm Infection

The larval or mature stages of tapeworms can affect humans. The larval stage may be harbored in any human organ, while the mature forms live in the intestine. Though there are over 30 species of tapeworms producing intestinal infection in man, the most important are *T. saginata* (beef tapeworm), *T. solium* (pork tapeworm) and *Diphyllobothrium latum* (fish tapeworm). The intestinal infection is acquired by eating uncooked meat or fish harboring the cysts.

Symptoms due to intestinal infection with *T. solium* and *T. saginata* are few and consist of nonspecific abdominal distress. Usually the patient becomes aware of the parasite when the distal proglottids come out through the anus, making the host socially uncomfortable. The patient

usually harbors only one worm. Eosinophilia may be present. *Diphyllobothrium latum* (fish tapeworm) infestations are usually multiple and produce more nonspecific abdominal symptoms. In addition, a few patients develop a megaloblastic anemia due to the increased avidity of the worm to fix vitamin B₁₂ from the intestinal tract.

The diagnosis of tapeworms is usually made from the extruded proglottids brought by the patient. The stool examination reveals the characteristic eggs of the tapeworm.

The drug of choice in intestinal tapeworm infections is quinacline hydrochloride (Atabrine, mepacrine). The patient should be placed on a liquid diet the day prior to treatment and left fasting after the evening, when a soapsuds enema should be given. Without breakfast the quinacline hydrochloride is administered in two divided doses, half an hour apart to minimize vomiting. The total adult dose is 0.8 gm. Children weighing from 40 to 75 pounds receive 0.4 gm., those from 76 to 100 pounds 0.6 gm. Two hours after the last dose a saline cathartic is administered. The patient should stay in bed and all feces should be collected for examination. In *T. solium* and *T. saginata* infections the recovery of the scolex (head) usually indicates successful treatment.

The main complication of treatment is vomiting of the administered quinacline. This can be obviated only by duodenal instillation of the drug. One treatment is usually effective.

Oleoresin of aspidium (male fern), though effective, has been gradually abandoned because of its toxicity. A comparative study of the use of male fern and quinacline revealed that they are about equally effective. In about 80 per cent of the cases cure was effected by one treatment.²³

Iodoalaphionic acid (Priodax), used as a contrast medium in x-ray visualization of the gallbladder, has been reported as an effective drug in the treatment of tapeworm in children without producing vomiting.²⁰ The use of tablets containing metallic powdered tin, tin chloride and stannous oxide administered for five days after meals eradicated the tapeworms in 90 per cent of the cases.⁹ Another approach to the treatment of taenia is the DeRivas method of the instillation in the duodenum of magnesium sulfate, glycerine and physiological saline solutions warmed to 130° F. The treatment seems to be effective and harmless, but requires duodenal intubation.¹⁹ Naturally, the treated patient should be given pertinent instructions to cook food well to avoid reinfections.

The larval stage infection of man (visceral cestodiasis) presents difficult diagnostic and therapeutic problems. The main offenders are *T. solium* and *Echinococcus granulosus*. The diseases are acquired by the ingestion of the ova, which hatch in the gastrointestinal tract, producing a larva which migrates through the intestinal wall and becomes encysted in any region of the body. The only available treatment is surgical excision of the cysts.

TREMATODE INFECTIONS

Schistosomiasis

Schistosomiasis is one of the most prevalent diseases in the world. Three species are responsible for almost all human infections. *Schistosoma*

mansoni is found in Africa, Asia Minor, the West Indies and in northern regions of South America. *Schistosoma haematobium* is found in Africa and Asia Minor, and *S. japonicum* in the Far East. Any inhabitant or visitor to an endemic area who has come in contact with fresh water streams is a potential candidate for the infection.

Usually the penetration of the cercaria through the skin is unnoticed by the patient. Occasionally some persons experience transitory itching and may develop erythema and wheals at the site of entry. The schistosomules enter the venules and lymphatics of the human host and gain access to the lungs, at times producing cough. They are distributed throughout the body by the circulation, reaching the mesenteric venules where they reach productive, sexual maturity. About four to seven weeks after infection oviposition begins.

In a minority of patients the period of initial oviposition may be accompanied by an acute disease characterized by fever, skin rashes, headache and diarrhea, at times with blood. Splenomegaly, hepatomegaly, lymphadenopathy and eosinophilia are usually present. The symptoms may last for a few days to over eight weeks.⁴

The chronic disease may be asymptomatic with no demonstrable abnormality in the patient except the presence of the schistostome ova. In schistosomiasis haematobium the symptoms are mainly dysuria and hematuria, while in schistosomiasis mansoni and japonicum they are usually referred to the gastrointestinal tract. Dyspepsia, diarrhea, anorexia, heaviness in the abdomen, malaise, loss of pep and weight loss may occur.

Abundant and prolonged oviposition in the portal system may lead to portal hypertension, the inflammatory reaction to the ova producing an obstructive endophlebitis. The spleen becomes congested, collateral abdominal circulation develops and ascites may appear. The splenomegaly may be accompanied by evidence of secondary hypersplenism. Esophageal varices may rupture and produce massive bleeding. If malnutrition accompanies the disease, cirrhosis of the liver may become evident.

Schistosome ova may be carried to other organs of the body by the normal or enlarged venous collateral circulation. In the lungs extensive egg embolization with endarteritis may eventually lead to pulmonary hypertension and chronic cor pulmonale. Involvement of the spinal cord is not unusual in schistosomiasis japonicum. Many organs in the body may disclose the presence of the ova.

The diagnosis is confirmed by finding the characteristic ova. In schistosomiasis haematobium the ova may be recovered from the urine or the stools. In schistosomiasis mansoni and japonicum the ova can be found in the stool. As one stool examination may miss 50 per cent of the cases, it is recommended that at least three stool examinations be done. The ova can be also demonstrated in biopsies of the rectum, bladder and liver.

Cutaneous tests with cercarial and adult worm antigens are useful. They are simple to perform but a good, well standardized antigen should be used. The injection of the antigen produces a wheal and erythema

reaction in 15 to 30 minutes in 80 to 90 per cent of those who have the disease. Serological tests as complement fixation, slide flocculation, and circumoval precipitation may be used to confirm the diagnosis with about the same efficiency as the skin tests.

The treatment of schistosomiasis has been unrewarding.⁵ The available drugs are either ineffective or too toxic.

Antimonial compounds have been used, with results of therapy which are variable from one series to the other, but probably the cure rate is less than 50 per cent. These drugs are capable of producing severe reactions and must be administered under continuous medical supervision. The two most widely used drugs of this class have been tartar emetic (potassium antimony tartrate) and stibophen (Fuadin). The general impression is that tartar emetic is more effective than stibophen, but it is more toxic and has the disadvantage of having to be administered intravenously. Sudden death may occur with both drugs. Undesirable reactions include anorexia, nausea, vomiting, headache, arthralgias, myalgias, cutaneous eruptions, myocarditis, convulsions, shock and hematological disorders as thrombocytopenia and hemolytic anemia. Often side reactions require discontinuation of treatment or diminution of doses.

Stibophen is probably the drug most widely used today for the treatment of the disease. It is administered intramuscularly in a 6.3 per cent solution and as follows: 1.5 cc. on the first day, 3 cc. on the second day, 5 cc. on the third day, 5 cc. on the fifth day and 5 cc. every other day to complete 90 to 120 cc. The course can be repeated three months after completion.

Tartar emetic is administered intravenously. A freshly prepared sterile solution of 0.5 per cent of tartar emetic in 5 per cent glucose in physiological saline is given slowly intravenously as follows: 8 cc. on the first day; 12 cc. on the third; 16 cc. on the fifth; 20 cc. on the seventh; 24 cc. on the ninth; 28 cc. on the eleventh day and thereafter 28 cc. every other day to complete 380 cc.

Miracil D, a thioxanthone, is used orally in daily doses of 10 mg. per kilogram of body weight for 12 days. Abdominal cramps, nausea, vomiting and yellow discoloration of the skin may occur. The drug seems to work better in *S. haematobium* infection.

The patient with schistosomiasis should be placed on a good diet as there is evidence that good nutrition decreases the hazards of the disease. He should avoid reinfection. If there is hypersplenism, splenectomy may alleviate the hematological alterations. If bleeding varices are present the patient should be treated accordingly. Portacaval shunts seem to decrease the incidence of bleeding esophageal varices, but they may increase the incidence of bleeding peptic ulcers and hepatic coma. Long follow-up is required in these patients and a controlled series is needed to evaluate the effect of surgery. The treatment of pulmonary schistosomiasis is symptomatic and supportive.

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The Status of Immunization in 1963

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INTRODUCTION

DURING the 9 years since our second resume on immunization⁸⁸ rapid advances and changes have continued in all disciplines of medical science including immunology. Even though more antibiotics are available for the treatment of bacterial infections these drugs have definite limitations and disadvantages.⁹⁰ We must continue to investigate and utilize vaccines for protection against most of the viral diseases. Unlike chemoprophylaxis, immunization frees man from having to take a drug regularly. It converts a susceptible person into a resistant one, enabling him to move wherever or whenever he chooses carrying his protection with him. To quote Edsall:⁴² "Never in the history of human progress has a better and cheaper method of preventing illness been developed than immunization at its best."

Prevention of disease continues to be our most important goal. The practice of maintaining an active and up to-date immunization program becomes more and more important as the number of effective agents increases. The object of immunization is to produce without harm a degree of resistance in individuals as great as, or greater than, that which follows the natural infection.²⁴ In the past decade, two more live vaccines (poliomyelitis, measles) have been produced and shown to be very effective. It is against the diseases of viral origin that immunization procedures have been most effective. The value of BCG vaccine for the

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One very important area which needs continued emphasis by the physician is the administration⁵³ of these vaccines to as many patients as possible on a private and community basis. With so much emphasis on civil defense measures, little will be gained from a preventive medical aspect if these vaccines are not adequately utilized. Recent surveys have shown very low immunization rates particularly in adults over 30 years of age. The major problem is to overcome public apathy,³² get the vaccines into people who need them and to record properly this data on the patient's health record.³⁸ An adequate immunization and personal health record* recently revised by the Public Health Service if kept by all would fulfill this requirement.

The infectious diseases against which immunizing procedures are available are divided into the following groups:

- I. **Those which are mandatory**, i.e., those in which there is no satisfactory method of control other than by vaccination (smallpox, tetanus, diphtheria, pertussis, poliomyelitis, influenza, measles, pediatric schedules).
- II. **Those which are mandatory under certain circumstances**, i.e., those in which vaccination would be limited to certain areas or occupational groups; and those which prophylactic vaccination would be useful along with other control measures (typhoid, epidemic typhus, cholera, rabies, plague, tuberculosis, yellow fever [see also overseas map]).
- III. **Those in which vaccination is advisable in certain areas or occupational groups** (in conjunction with other control measures) (adenovirus, mumps, Q fever, Rocky Mountain spotted fever, tularemia).
- IV. **Those which are of passive value or are under study** (anthrax, brucellosis, dengue fever, infectious hepatitis, gamma globulin, leptospirosis, rubella, trachoma).
- V. **Those which are not advisable** (scarlet fever, encephalitides, endemic and scrub typhus, bacterial vaccines, poison ivy vaccines, cold, staphylococcus and acne vaccines).

GROUP I. DISEASES AGAINST WHICH IMMUNIZATION IS MANDATORY

Smallpox

Even though Edward Jenner demonstrated the value of vaccination 165 years ago in Gloucestershire, routine vaccination is not practiced in England. In fact, much controversy presently exists in Great Britain as to the necessity of universal smallpox vaccination.⁴⁰ This procedure is still first in importance, and the vaccine is one of the most effective immunizing agents.⁴¹ Its protective efficacy was well demonstrated in 1960 with the swift suppression of a smallpox outbreak in Moscow when 9 million persons were immunized during one week.¹⁵⁶ This efficacy was also noted by Weinstein in New York City in 1947.¹⁵¹

The effectiveness of proper vaccination was shown during World War II² by the occurrence of only 105 cases of smallpox in the Armed Forces. Most of these patients were in the Orient where smallpox was prevalent.

* International Certificate of Vaccinations. P.H.S. 731, revised 6/61.

An investigation of these failures of vaccination showed that most were attributed to faulty vaccination technique or intense sensitization reactions incorrectly interpreted as primary reactions.¹¹¹

The necessity of primary and repeated revaccination at proper intervals was poignantly illustrated by the recent outbreak of 12 cases in Bradford, England when 6 deaths occurred.³⁶ The importance of proper interpretation and recording of the results of vaccination were emphasized when it was ascertained that the 9 year old Pakistani girl who flew from Karachi 2 weeks before and presumably transmitted the disease, had an apparent immediate reaction on revaccination. Having been vaccinated only once during infancy, her first booster (revaccination) had been given less than 4 weeks prior to her death.

In this country primary vaccination is routinely advised prior to 1 year of age since postvaccinal encephalitis almost never occurs in this group. Interestingly, primary vaccination is preferred at ages 1 to 4 years in Great Britain since complications there have been more common in the infant under one year of age. The technique of vaccination is important (Table 1).

INTERPRETATION OF THE RESULTS OF VACCINATION. The proper time to read the vaccination is between the seventh and ninth day since differentiation of the three types of reaction is based on the time at

Table 1. Immunization Against Smallpox

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
1. Smallpox vaccine U.S.P. Live cowpox virus—fluid glycerinated. Potency period 3 months. Store at freezing temperatures.	All—particularly before travel to other countries.	Cleanse skin with acetone or ether. 10 to 30 multiple pressures with needle held parallel to skin on area 0.25 cm. in diameter over the insertion of the deltoid muscle.	Three to four years. Medical and Armed Forces personnel should be revaccinated every 3 years.
2. Lyophilized (freeze-dried) smallpox vaccine stored in cool space. Potency period, 18 months.	May be given at 1 month of age if travel necessary.	Use a generous amount of vaccine. Bleeding should not occur.	
REQUIRED REPEAT VACCINATIONS AND CONTRAINDICATIONS TO VACCINATION			COMMENTS ON REACTIONS
<i>Vaccinate:</i>			<i>Early, Immediate or Allergic Reaction</i>
1. Quadrennially (Leap Year). 2. Whenever exposed to smallpox. 3. In presence of an epidemic. 4. If doubt exists as to reaction of a previous vaccination. 5. Annually if residing in an endemic area.			Itching, erythema or even vesicle appears but regresses by 4th day, leaves no scar. Reaction can be elicited by inert vaccine so indicates immunity only if vaccinoid or vaccinal reactions are obtained concurrently in other individuals.
<i>Delay Vaccination in Patients:</i>			<i>Accelerated or Vaccinoid Reaction</i>
1. With eczema or whose siblings have eczema. 2. With septic skin conditions. 3. With acute febrile conditions. 4. Recently exposed to common contagious disease. 5. With conjunctival ulcers. 6. With general debility. 7. In first 6 months of pregnancy in absence of a smallpox epidemic.			Maximal area of erythema and vesicle attained by 4th to 7th day. Immunity has been restimulated.
			<i>Primary Reaction or Vaccinia</i>
			Maximal area or erythema usually attained 8th to 12th day. Vesicle always seen and progresses through stages of pustule, crust and scarring. Individual is now protected.

which the areola reaches the maximum redness and not upon the presence of a scab.

1. *Primary Reaction.* A large area (10 to 12 cm.) of redness is expected between the eighth to twelfth day. A vesicle always occurs followed by pustulation, crusting and scar formation. This reaction indicates complete absence of previous immunity. Fever, malaise and regional lymphadenopathy are expected at the height of the reaction and occasionally erythema multiforme is observed.

2. *Vaccinoid (Accelerated) Reaction.* This reaction occurs in those who are partially immune. Maximal erythema (4 to 6 cm.) is usually attained in 4 to 7 days. A papule followed by a vesicle usually occurs within 24 to 48 hours. Scar formation is produced but may be difficult to find later. Systemic manifestations are minimal.

3. *Early (Allergic) Reactions.* This is seen in the immune person or it may indicate nothing more than sensitization to viral protein from primary immunization or disease. This reaction may occur when deteriorated vaccine or poor technique are used. Therefore, one must consider revaccination depending upon the history of the patient or possibility of exposure to smallpox infections. The maximal area of erythema develops between 8 and 72 hours and is only 1 to 2 cm. in diameter. A vesicle may appear with ultimate scabbing but no scar formation. If no reaction occurs, a repeat vaccination must be done. Repeated failures should direct one to vaccinate on the other arm or the flexor surface of the forearm.

Thus in order to fulfill the object of primary vaccination with smallpox, i.e., to create a local cutaneous infection, one must produce a major vaccinia reaction. This means that the results of the vaccination must be read on the seventh to ninth day and properly recorded in the immunization certificate. If a minor reaction occurs following primary vaccination, a second vaccination must be accomplished and re-examined 7 days later.

CONTRAINdications TO VACCINATION. 1. Children or adults with eczema, impetigo or other forms of dermatitis (not diaper rash) should not be inoculated because of the danger of eczema vaccinatum. If an individual with these conditions is accidentally exposed to vaccinia virus then vaccinia immune gamma globulin should be administered intramuscularly in dosage of 0.3 ml./kg. of body weight. Similar measures for passive protection of an eczematous person who must go to an area where smallpox is endemic can be used. The individual can be vaccinated and 12 to 24 hours later hyperimmune gamma globulin given to abort the expected eczema vaccinatum.¹

2. Siblings of children with extensive dermatitis or eczema should not be vaccinated for the above reason unless the sibling to be vaccinated can live in a separate building until the scab falls off.

3. Premature infants or persons on steroid therapy with general debility such as leukemia should not be vaccinated.

4. During the first 6 months of pregnancy vaccination should be withheld⁴⁹ unless an epidemic situation develops.⁷²

5. Patients with recent exposure to a contagious disease, conjunctival lesions or inflammation or an acute febrile illness should not be vaccinated.

6. Patients with gamma globulin disorders should be carefully evalu-

ated prior to vaccination. Space does not permit discussion of faulty immune mechanisms, the production of vaccinal antibodies in such patients¹⁰ and the effectiveness of using hyperimmune antiserum as demonstrated by Kempe's studies.¹¹

COMPLICATIONS. The incidence of adverse reactions is low in this country compared to those in Great Britain noted by Gaisford.⁵⁹ There appears to be variation from country to country depending upon the age at which primary vaccination is done.⁶³ Certainly vaccinia should not be considered as an adverse reaction in an unimmunized person. The two most serious complications are postvaccinal encephalitis and eczema vaccinatum. The former is rarely seen in the United States. Eight cases were reported during World War II and only 4 were subsequently proved to be due to smallpox vaccination. Encephalitis is much less frequent after revaccination unless more than 10 years have elapsed.⁶³ Acute renal failure,⁵⁶ infectious polyneuritis,⁸³ and myocarditis¹⁸ have been reported.

Generalized vaccinia is a very serious complication and will rarely occur if one avoids inoculation of persons with skin disorders such as eczema or atopic dermatitis. This condition and progressive vaccinia which occur in children who have an inability to produce antivaccinal gamma globulin should be treated with vaccinia immune globulin in dosage of 0.6 ml./kg. body weight. Additional doses may be necessary at 1 to 2 week intervals. This preparation is available through the Regional Blood Centers of the American Red Cross.

IMPORTANT POINTS IN MANAGEMENT (see also Table 1).

1. A successful vaccination should be produced in all infants before 1 year of age.
2. Use a potent vaccine. Freeze-dried material (Dryvax, Wyeth) is preferable because of its demonstrated superiority in initial antigenicity, prolonged potency (18 months) and simplicity of storage (2° to 10° C.).
3. Be sure all acetone or ether has completely evaporated before vaccinating.
4. Allow no occlusive shields or dressing. In pustular stage a loosely attached dressing is permissible if absolutely necessary.
5. Always interpret the vaccination on the seventh to ninth day.
6. Revaccinate in all cases of failure especially in infants less than 1 year of age to avoid postvaccinal encephalitis.

Tetanus

Since the introduction of tetanus toxoid as an immunizing agent in this country in 1933 the vaccine has proved to be one of the most effective and innocuous of all antigens. Therefore, since tetanus may occur in any person at any age, tetanus immunization should be universal. Its efficacy was sternly tested during World War II and in Korea. Despite the fact that many soldiers were severely wounded and in shock for prolonged periods, only 4 cases of tetanus occurred among U.S. soldiers who had been fully immunized and had received an emergency booster at the time of injury.²

Recent studies^{68, 126} have shown that a protective level (over 0.1 unit) occurred in 100 per cent of servicemen within 3 weeks following a booster even though the last booster had been given 14 to 18 years previously. In many cases protective antibody levels developed within 1 to 2 weeks after a booster. In view of the frequency of automobile, household and recreational accidents, it is particularly important to maintain quadrennial boosters so that in the event of an accident a booster would elicit protective antibodies within 5 to 7 days and thereby avoid the use of tetanus antitoxin. Edsall⁴⁴ noted that if everyone today were properly immunized with tetanus toxoid the disease would not occur except in the rare individual who cannot form antibodies.

Regarding tetanus-prone injuries, it is well known that minor injuries account for more than half of reported tetanus cases and occasionally no history of injury may be obtained. Therefore, all wounds should be thoroughly cleansed, debrided and a toxoid booster given unless the patient had one in the previous 12 months and the wound was trivial. An extensive or heavily contaminated wound demands an immediate booster (0.5 ml.). For patients who have received proper primary tetanus immunization within the previous 5 to 10 years a booster will produce an excellent antibody response within 5 days.⁴⁴ In these patients, regardless of the type of injury, the booster will provide ample protection if it is given within 24 hours, but if more than 24 hours have elapsed and the injury is extensive or heavily contaminated, then, regardless of the age of the individual, 5000 units of tetanus antitoxin (T.A.T.) should be given at the same time in a different extremity.

When the interval since the last toxoid booster is over 10 to 15 years, the physician must carefully weigh the facts: (1) a reliable history of primary tetanus immunization; (2) time elapse since injury; (3) type of injury; (4) allergic past history; (5) previous T.A.T. or other horse serum injections. Certainly if a history of basic immunization is equivocal, the wound is massive with the risk of tetanus being self-evident, or a delay of over 24 hours has occurred then T.A.T. must be administered. In the event that fluid toxoid is available it is preferable to the depot toxoid since it may induce a slightly faster response.⁴⁴ If horse serum allergy is known or detected by skin testing, or T.A.T. (equine) has been given previously, then bovine or preferably human tetanus antitoxin¹³⁹ must be given. If 48 hours have elapsed, 10,000 units or more may be indicated depending upon the circumstances.

Prompt administration of T.A.T. (10,000 to 20,000 units) is recommended for all patients with massive wounds or those with potentially contaminated wounds over 24 hours in duration who have not previously had active immunization with tetanus toxoid. At the same time it is advisable to administer the first dose of toxoid in a different extremity. The heterologous antitoxin must be repeated within 1 week after sensitivity testing if the wound is not clean and healing.

The use of homologous instead of heterologous antitoxin should eliminate the need for a second dose since the half life of the homologous antitoxin (gamma globulin) is 4 weeks, in contrast to 1 week for equine T.A.T.¹³⁹ As this preparation becomes more available it will eliminate

the danger of serum sickness and anaphylactoid reactions, which varies from 5 to 15 per cent.

When using equine T.A.T. the physician must inquire about sensitivity to horse serum, history of allergy and administer preliminary dermal and ophthalmic tests for sensitivity. A tourniquet and syringe with 1:1000 epinephrine should be immediately available. The routine skin test dose is 0.1 ml. of a 1:100 saline dilution of the serum injected intracutaneously, but if a history of allergy is obtained the dose must be reduced to 0.05 ml. of a 1:1000 dilution of the serum. Fatal anaphylactic shock has occurred with a 1:10 dilution.¹⁴ An extensive review of serious complications from T.A.T. by Bardenwerper⁵ should convince every physician to actively maintain tetanus immunity in all patients.

Penicillin (600,000 units daily for 10 days) or 2.4 million units of benzathine penicillin G (Bicillin, Wyeth) or erythromycin (1 gm. in divided doses daily for 10 days) is recommended for all persons hypersensitive to T.A.T., or who have previously received T.A.T. and are treated within an hour or two after injury.² Antibiotics are indicated in instances of: (1) extensive or contaminated wounds; (2) profound shock; (3) delay or difficulty in proper wound debridement. They should never be used as a substitute for proper debridement or for antitoxin. Filler and Ellerbeck⁵² have recommended that the nonimmunized patient receive only local care for trivial wounds treated promptly, but that benzathine penicillin G be given if the wound is more extensive or contaminated. They would reserve tetanus antitoxin for massive wounds or those moderately contaminated ones seen 48 hours after injury. Since penicillin-resistant strains of *B. tetani* are known to exist, one must be cautious in following this plan.

Table 2. Immunization Against Tetanus

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
1. Tetanus toxoid depot (alum-pptd.) U.S.P. 7.5 ml. vial. Potency period 24 months. Store at 35.6° to 50° F. (2° to 10° C.)	1. All persons particularly military personnel, farm workers, and those in occupations associated with horses.	1 and 2. Two 0.5 ml. doses IM at 1 to 2 month intervals. A third (reinforcing) 0.1 ml. dose SC or IM is given 12 mos. after the second.	Prolonged at least 5 years.
2. Tetanus and diphtheria toxoids combined (precipitated absorbed), adult use, 5 ml. vial. Potency period 24 months.	2. Allergic persons, those with chronic skin ulcers and those who have had tetanus antitoxin or horse serum.	3. Three 0.5 ml. doses at 1 month intervals.	Satisfactory anamnestic response to booster dose 10 to 15 years after initial series.
3. Tetanus toxoid, fluid.			

REQUIRED REPEAT INOCULATIONS

COMMENTS

1. Routine booster dose: 0.1 ml. 1 year after initial series. Repeated quadrennially (Leap Year) with 0.1 ml. toxoid SQ or IM.	Persons who have not received toxoid immunization and in whom passive immunization is necessary should be started on active immunization at the same time by simultaneous injections of T.A.T., 5,000 to 10,000 units, and tetanus toxoid in separate extremities.
2. Emergency booster dose: 0.5 ml.	In severe injuries with prolonged shock or if treatment is delayed 24 hours, simultaneous inoculations of 10,000 units of T.A.T. and toxoid booster separately may be advisable in debilitated or partially immunized persons. If treatment is prompt a toxoid booster will suffice.
a. Upon incurring punctured or lacerated wounds, animal bites, burns or other contaminated wounds.	
b. Upon undergoing secondary operations or open manipulations when contamination with tetanus bacilli or spores is likely.	
c. All wounds should be properly debrided and cleansed promptly. If more than 3 hours elapses prior to local therapy, give booster even if wound is trivial.	

The indications for tetanus toxoid active immunization are: (1) routinely for all people at all ages; (2) to confer passive immunity against neonatal tetanus upon the infant through active immunization of the pregnant mother. Schofield et al.¹³⁴ showed that 3 injections provided substantial protection against the risk of neonatal tetanus.

A plea for nationwide tetanus toxoid immunization was recently made³⁹ based upon an excellent communication by Furste et al.⁵⁸ The disturbing fact that 46 per cent of females and 28 per cent of males over 18 years of age had not had tetanus immunization was noted. In contrast, as a result of effective prophylactic programs carried on by the general practitioner and the pediatrician, only 8 per cent of females and 4 per cent of males under 18 years were not actively protected. A further appeal was made to continue boosters and have the patient carry this information in his own health card obtainable from the American Medical Association.

Reactions to the alum-precipitated toxoid are minimal (1 to 2 per cent), especially if the injection is given intramuscularly and followed by 0.1 ml. of air. Doses, and booster intervals are noted on Table 2. A discussion of tetanus-diphtheria toxoids combined, precipitated, absorbed (for adult use) is found in the section on diphtheria.

Diphtheria

Despite the fact that almost 40 years have elapsed since diphtheria toxoid came into general use, diphtheria remains a constant menace. In contrast to the overall downward trend since 1927, a slight increase in cases occurred in the southern states during 1958 through 1960. The case fatality ratio has shown relatively little change even with the availability of antibiotics, antitoxin and specialized medical care. Therefore it behooves all physicians to see that basic diphtheria immunization is performed and boosters be administered quadrennially.

A study of 873 patients with diphtheria in the United States during 1960³⁵ reveals that 72 per cent had received no immunization, 9 per cent had a primary series but improperly spaced boosters, and only 10 per cent were fully immunized. A single death due to myocarditis occurred in the primary series group. This occurred in a 35 year old diabetic who received a primary series at 9 years of age. Sixty-eight per cent of this group had mild cases compared to 54 per cent of persons with no history of immunization. Fifty-seven deaths occurred among persons without a primary series. About 80 per cent of the cases occurred in children under 15 years of age. Bacteriological confirmation was obtained in 75 per cent of the patients.

A natural decline in diphtheria has occurred during the past 30 years in many countries,²⁴ but none is so dramatic as that in Denmark, from 23,000 cases to as few as 1 case per year. Clinical experience has so established the effectiveness of diphtheria immunization in decreasing morbidity and mortality that it is a fully accepted procedure in the practice of medicine. That it has not been given to certain groups is evidenced, however, by more than 130 cases in the 1956 Detroit epidemic. Many of these patients were from one part of the city where the population consisted of large numbers of low income persons from the South. In only 1 case had a primary immunization with a booster dose been given. Therefore, at times when our control measures lapse and the percentage of nonimmune persons in the population rises, an epidemic may ensue. It is

known that diphtheria can be brought under control in a community when some 70 per cent of the children (1 to 15 years of age) are effectively immunized. In addition, in those areas where the natural disease has been markedly reduced, boosters should be given every 4 years since the previous recurring antigenic stimulus has been removed.

With the availability of adult tetanus-diphtheria (TD) toxoid the Schick test has been relegated to evaluation studies and is rarely used otherwise. The effectiveness of small doses of adult TD antigen in soldiers was proved by Cooch and Greenberg²² when only 8.4 per cent were found to be Schick-positive after basic training. Three months later only one-third of this group was still positive although no immunization had been performed in the interim. In another study⁴¹ on adults only 50 per cent were found to be Schick-negative (immune). The problem of hypersensitivity to diphtheria toxoid in adults has been solved by the administration of relatively small doses of toxoid. These small doses have been incorporated into a standard preparation which contains the usual amount of tetanus toxoid and to which has been added 2 Lf doses of purified diphtheria toxoid per ml. After 3 properly spaced doses of this material 95 per cent or more of adults are found to be immune; after 2 doses, 80 per cent are immune. This combination eliminates the necessity for separate diphtheria and tetanus immunizations unless sensitivity to the latter has been demonstrated. If adult TD is not available, Schick testing must be done prior to inoculation of standard (10 to 20 Lf) diphtheria toxoid. Toxoid sensitivity testing (Moloney) is also unnecessary when using the adult TD preparations. Although diphtheria toxoid is one of our best antigens, it has never proved to be 100 per cent effective. Dunnet et al.³⁷ report the death of an 8 year old who had received his booster $3\frac{1}{2}$ years previously.

All persons should be immunized against diphtheria beginning in early infancy. Although studies have shown that newborn infants respond to an antigenic stimulus, a higher and more persistent titer will occur if the series is started between 4 and 8 weeks of life. Many studies have shown that while passive immunity in the young infant does exert some "blocking" effect against antibody production of diphtheria, pertussis and recently poliomyelitis,⁶ it is not of sufficient importance to withhold these immunizing agents until 5 or 6 months of age. Further discussion on triple depot antigens will be found in the pediatric section.

With the antigenic superiority of the alum-precipitated toxoids and the rapid development of protective antitoxin levels within 2 months which are sustained for several years with a second and booster dose, the need for diphtheria antitoxin should rarely occur. If the patient has not been immunized previously and a clinical diagnosis of diphtheria is made, antitoxin and penicillin must be given before bacteriological confirmation can be made. The dose (20,000 to 75,000 units) depends upon the site of the membrane, the degree of toxicity and the duration of the illness.¹ After skin testing the antitoxin is usually given intramuscularly, but it is given intravenously if toxicity is marked or the patient has been ill more than 48 hours. Exposed susceptibles who can be observed are not given antitoxin. Cultures are made and they are started on

Table 3. Immunization Against Diphtheria (For Adults)

IMMUNIZING AGENT	ADULT RECOMMENDATIONS	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
1. Tetanus and diphtheria toxoids combined, precipitated absorbed (adult use), 5 ml. vial. Potency period 24 months at 35.6° to 50° F. (2° to 10° C.).	For all individuals unless Schick-negative. However use of adult TD obviates the need for Schick or Moloney tests for toxoid sensitivity.	Two 0.5 ml. doses intramuscularly 1 to 2 months apart, but not over 4 months. A third (reinforcing) injection 0.1 ml. is given about 12 months after the second. Adult TD preferred to avoid Schick or toxoid sensitivity tests.	Four to five years, but partial protection probably lasts for years.
2. Diphtheria toxoid alum-precipitated (if sensitivity to tetanus toxoid demonstrated).			
REQUIRED REPEAT INOCULATIONS			COMMENTS
<p><i>Routine booster:</i> 0.1 ml. IM recommended quadrennially. Combined tetanus-diphtheria toxoids (adult use) to be used if basic immunizing series has been given.</p> <p><i>Emergency booster:</i> 0.5 ml. IM. Give for exposure to diphtheria or suspected disease.</p> <p>Do not use pediatric TD toxoid in persons over 10 years of age.</p>			If adult type TD is not available, Schick test itself may convert previously immunized patient reacting positively to negative. Recheck with second Schick test in 3 weeks if practicable. If pronounced sensitivity is elicited by Moloney test, do not immunize. The occurrence of local edema, induration or erythema more than 6 cm. in diameter after any dose in the series, or marked constitutional reaction with fever over 101° F., is a contraindication to further doses of the toxoid.

penicillin therapy, then given a recall injection or their first dose of depot toxoid. Severe reactions to a test dose or to any injection of the series would contraindicate further immunization. Constitutional reactions have been minimal (1 to 2 per cent).²

Local reactions such as sterile abscesses are unusual especially if the intramuscular injection is followed by 0.1 ml. of air to empty the needle. Table 3 outlines the methods of immunization.

Pertussis

In the period 1940-1948 whooping cough killed 3 times as many infants under 1 year of age in the United States as rubeola, mumps, varicella, scarlet fever, diphtheria, poliomyelitis and meningitis combined.²⁴ The severity of the disease in the catarrhal stage may be lessened by the use of antibiotics and gamma globulin,⁶¹ but since presently available vaccines afford as high as 85 to 90 per cent protection,⁴¹ the health officer will logically elect to immunize actively all infants against pertussis between 4 and 8 weeks of age.

Studies performed under the auspices of the British Research Council since 1951 have established that the present vaccines (purified antigenic Phase I fraction of *Bordetella pertussis*) are potent and safe. With standardization of an acceptable level of potency of the vaccines by the intracerebral challenge mouse protection test and adoption of 12 antigenic units as a total immunizing dose, recent controlled field and laboratory trials with present vaccines have shown a considerable degree of protection. Twelve antigenic N.I.H. units (1.5 ml.) of the fluid vaccine is not less in potency than 90,000 million bacteria of the N.I.H. standard pertussis vaccine. The alum-absorbed toxoid contains about

48,000 million organisms in 1.5 ml. since it produces a higher agglutinin titer than the plain vaccine, particularly when combined with diphtheria and tetanus toxoids.

Since our last review Cockburn²⁰ and Strom¹⁴³ discussed the problem of severe and rarely fatal reactions following pertussis vaccination. Prior to the ceiling (with top and bottom limits) being placed on the antigenic content of pertussis vaccine, 11 postvaccinal deaths were reported (1944-1952), but none has occurred since then.⁴¹ In spite of this, any infant with cerebral dysfunction or repeated seizures should be over 1 year of age before starting pertussis vaccine. In such infants single rather than multiple antigens are recommended and fractional doses should be employed.¹ Acetylsalicylic acid, 65 mg. per year of age, up to 324 mg. total, may be given within 4 hours of the injection and repeated every 4 hours as indicated. Cockburn²⁰ concluded that the disease is a serious one, and even though the risks involved in vaccination are real, they are much smaller.

Early vaccination of infants was recommended by Kaufman and Bruyn⁸² in a recent study of 199 children with pertussis of which only 13 had been completely immunized. Despite a forty-fold decrease in cases reported since 1930 in the state⁴⁵ (10,750 in 1930 to 251 cases in 1961), the Massachusetts Institute of Laboratories* continues to study methods to improve the vaccine and standardize its potency. During this same period in Massachusetts deaths from pertussis decreased from 182 in 1930 to 22 in 1940, to 11 in 1950, and to only 1 in 1960. Other rare complications of vaccination that have been reported are purpura and allergic edema. A discussion of the nature of the cerebral reaction may be found in Lamm's text.⁸⁶ Certainly a severe febrile reaction with or without convulsions would direct one to delay the series of inoculations for 2 months. One would then try 0.05 to 0.1 ml. doses of plain pertussis vaccine, using antipyretics at 4 hour intervals for 24 hours.

Recent studies in England¹⁷ and the U.S.⁶ have shown that the neonate and young infant can produce significant antibodies which afford protection against pertussis. This occurs whether pertussis vaccine alone is given during the first 6 weeks of life or given as the combined D.P.T. toxoid starting at 2 to 3 months of age followed by a booster 6 to 12 months later. Interference with antibody formation does not occur since the newborn is devoid of passively transferred maternal antibodies. In communities having a low incidence of pertussis the vaccine may be delayed until 3 to 6 months of age, especially if the older siblings have been properly immunized. Routinely, the vaccine is given at 6 weeks of age as the D.P.T. toxoid consisting of 3 injections, 0.5 ml. each, at monthly intervals with a booster at 12 months of age.³

Fluid (plain, nonabsorbed) pertussis vaccine may be given any time after birth for the following circumstances:¹

1. To achieve rapid protection during the epidemics of pertussis: Three equal doses of 4 N.I.H. units (0.5 ml.) each may be given subcutaneously at intervals of one week. Greater and more prolonged protection will result if the intervals are longer, i.e., 3 to 4 weeks.

* Dr. G. Edsall, Superintendent of the Institute of Laboratories.

2. For recall injections to obtain rapid protection following exposure to pertussis.

3. For the older infant or child who has already been immunized with TD toxoid, especially the child with cerebral dysfunction or a history of seizures.

Recall injections are given at intervals of 2 to 3 years after the first booster at 12 to 18 months of age. There is probably little indication for maintaining active immunity to pertussis beyond 6 years of age,³⁸ although older children show little tendency toward severe reactions. Most physicians agree that immunization after 8 to 10 years of age is unnecessary since pertussis after this age is not likely to be severe.

Poliomyelitis

Ten years ago we wrote:³⁸ "Sabin has found virulent and nonparalytic producing mutants in his cultures and from these may be developed a vaccine of living virus that will prove satisfactory in producing prolonged effective immunity." Today over 150 million persons have received Sabin oral vaccine (S.O.V.) which has proved most satisfactory because of its safety, protective value and low reaction rate. In the interim about 500 million doses of Salk vaccine have been given with almost equal safety, protection and low reaction rate.⁶ Since the success and efficacy of the Salk vaccine have recently been reviewed^{141, 129, 150} these will not be discussed. The killed virus vaccine has undoubtedly more than fulfilled most medical authorities expectations with a sharp drop in the incidence of poliomyelitis since 1955.¹³⁰ A constant drop from an average rate of 30 (1949-1954) to about 1.5 cases per 100,000 for 1960 in the U.S., and from 27 to about 0.15 cases per 100,000 in Australia, Denmark and Sweden vouches for its effectiveness; however, it appears that the killed vaccine will be superseded by the more easily acceptable oral vaccine for the following reasons:^{24, 150}

1. *Antibody Response.* Batson et al.⁹ have shown that 80 per cent serological response occurred in 6 to 18 week old infants fed S.O.V. in the monovalent form at 6 week intervals. High levels of passive antibody of maternal origin did not interfere with production of active antibody. Pagano et al.¹⁰⁷ noted that maternal antibodies in prematures did not interfere with infection by CHAT type 1 live poliovirus vaccine nor was there obvious inhibition of active immunologic response. One hundred per cent serological response is possible if the vaccinees are over 6 months of age, are free from concurrent infections with other enterovirus, and the proper dose of vaccine and intervals are utilized.¹²⁹

2. *Rapidity of Immunity.* After a single dose of any of the 3 types of S.O.V. immunity can be produced in about one week.¹²⁹ This is most important in the young infant who may not respond to the killed vaccine.

3. *Ease of Administration.* People do not accept injections readily,^{38, 76} but will accept oral inoculations as evidenced by recent mass S.O.S. (Sabin on Sunday) campaigns which resulted in the vaccination of 90 per cent of the populace of several cities. Oral administration has eliminated the need for syringes, needles and sterilization equipment and has resulted in extensive coverage of all age groups owing to the simplicity of inoculation. The basic principles of the methods successfully used are outlined by Sabin.¹²⁹

4. *Vaccine Effectiveness.* The protection resulting from active immunity produced by the live vaccines has been well demonstrated in extensive field

trials¹²⁹ in Russia, Germany, Yugoslavia, South Africa, South America and in this country. In addition, these trials have shown how rapidly poliomyelitis can be eliminated from large populations. The immunity produced appears to be as good as after natural infections. The live vaccines probably induce cellular alterations in the intestinal mucosa similar to those of the natural disease, as predicted by Raffel.¹¹⁸

5. *Resistance to Reinfection.* The killed vaccine does not prevent enteric invasion by "wild" virus, whereas extensive multiplication of the live strains in the intestinal tract produces a local resistance to reinfection that is independent of the serum antibody. Thus, "wild" virus dissemination in the community is prevented. It is estimated that, if 70 to 80 per cent of the community is immunized, the "wild" strains would be unable to maintain themselves and, therefore, would be eradicated from that community.

6. *Immunizes the Unvaccinated (Herd Immunity).* As a result of spread of the virus from vaccinated individuals to nonimmune contacts,^{129, 150} another means is provided for the indirect protection of those who are not themselves vaccinated. Thus many adults, particularly parents, become immune by contact with vaccinated children.

7. *Safeness.* Until recently there were no reports that anyone had developed an illness due to live vaccines. In September 1962 Terry*,¹⁴⁵ and his advisory committee, after evaluating 13 cases of poliomyelitis which followed inoculation with type 3 oral polio vaccine (O.P.V.), concluded that 11 were possibly vaccine related. All patients were 16 to 52 years of age with 8 over 30, and there was a clustering of the intervals from vaccine feeding to onset within a 2-3 week period. Therefore the committee recommended that type 3 vaccine be restricted to children and high-risk adult groups. In December, 1962, after further study of these 11 cases and a few new ones, the committee concluded that no single case could be attributed to the vaccine. They recommended resumption of type 3 O.P.V. programs and emphasized the importance of immunizing all children; parents of young children; pregnant women; persons in epidemic situations and those going overseas. Terry's committee estimated that the maximal overall potential risk for types 1 and 3 was of the order of 1 per million or less, but higher for those over 30 years of age. There was no indication of risk for type 2 vaccine.

To date there are no reports of any deleterious effects upon the mother or fetus. There is some evidence, however minimal, of genetic instability of the vaccine in that an increase in neurovirulence has occurred in monkeys following inoculation of isolates of the attenuated virus from human feces. However, careful observations of contacts has not revealed any untoward reactions.

8. *Prevention of Epidemics.* Because of an early onset of immunity, the ability to interfere with naturally occurring poliovirus infections, and the ease with which mass immunization can be carried out in a very short time,¹⁵⁰ the S.O.V. has proved most successful in aborting several large outbreaks. One of the most dramatic results occurred in New York State in 1961. An epidemic was aborted in 2 weeks time after a massive 3 day campaign with oral vaccine. In the face of an epidemic Sabin¹²⁹ advises: (1) start early; do not wait until the epidemic is full blown; (2) give vaccine quickly within a few days, especially to children and their parents. The definition of an epidemic: the occurrence of at least 3 cases of poliomyelitis within 1 month, 2 caused by the same virus type.

9. *Durable Immunity.* Biennial doses of the killed vaccine are recommended¹ and some⁸ advise annual boosters depending on the commercial vaccine used, whereas antibody levels have been maintained for 8 years¹¹⁸ after basic O.P.V. immunization. It is not unreasonable to hope that immunity will persist for life.

* Surgeon General, U.S. Public Health Service.

Table 4. Immunization Against Poliomyelitis

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Poliomyelitis vaccine, oral, attenuated, Sabin, types 1, 2 and 3. Store below freezing 0° C. (32° F.). After thawing store at 35° to 50° F. (2° to 10° C.).	All infants over 6 weeks of age, children, young adults, medical personnel, pregnant women, parents with young children, all persons in epidemic situations and prior to overseas travel.	Oral, 2 drops or 2 ml. Monovalent vaccine at 6 to 8 wk. intervals. Type 1 first then type 3, type 2 last. Trivalent vaccine: 6 drops or 6 ml. 1 to 3 months later.	Prolonged at least 4 to 5 years.
REQUIRED REPEAT INOCULATIONS			COMMENTS
<i>Booster dose:</i> Trivalent vaccine, 6 drops or 6 ml., at time of epidemic to <i>all</i> persons using the "simultaneous saturation" technique. <i>Routine booster dose:</i> Unknown at present.			Thawed vaccine should not be used beyond the 7 day period. Do <i>not</i> refreeze thawed vaccine. Avoid inoculation in summer and during persistent vomiting or diarrhea. Vaccine may be given at 24 day intervals, with types 2 and 3 at one time, but trivalent vaccine must be given 1 to 2 months later.

The disadvantage of S.O.V. results from the interference phenomenon. Certain enteric viruses if actively multiplying in the intestinal tract at the same time that S.O.V. is given will interfere with the production of antibodies. If a mixture of all 3 types of poliovirus is given to nonimmune persons, infection with type 1 is readily suppressed by infection with the other types, and type 2 tends to overgrow in the presence of the other two. Therefore, each type is administered separately at 6 to 8 week intervals and type 2 is given last. In addition, one dose of the trivalent vaccine is given 1 to 3 months (or more) later to overcome any interference. The vaccine is best given during the late fall, winter and spring months to avoid the enteroviruses. One other disadvantage is that the vaccine must be stored in the frozen state, and the present shelf life after thawing is only one week.

Reactions have been nil and there are no known contraindications to the live vaccines. The amounts of antibiotics in a dose of oral vaccine are so small that hypersensitivity is not a contraindication.² The vaccines are propagated on monkey kidney tissue. The dose and intervals are noted on Table 4.

Influenza

Confusion still exists in medical circles as to the indication for influenza vaccination. Recommendations and commentaries⁷⁶ in medical journals have sometimes added to this dilemma especially when a flu epidemic is anticipated. The public is further confused by differences in policy and programs agreed upon by national groups but not reflected by local action at the community level.¹²²

In the past 20 years⁴¹ over 20 successful trials have shown the protective value of the vaccines. The average protection found after 18 experiments with types A,A₁ and Asian flu vaccines was 78 per cent (41 to 94 per cent) and after 4 trials using influenza B and B₁ vaccines

was 90 per cent (63 to 96 per cent). Only 2 vaccine failures occurred (1947 and 1955) in these studies. In these 2 years the vaccines given did not provide an antibody coverage sufficiently broad to cope with the strains then prevalent.²⁶ The Commission on Influenza of the Armed Forces Epidemiological Board reported that U.S. military personnel were relatively unaffected during 1960 by large outbreaks of influenza B among the civilian populace. They noted after a detailed analysis of strains currently prevalent that there was a common sharing of antigens, and it was shown that the vaccine presently used in the Armed Forces induced antibodies that are oriented against strains of the new subtypes of prevailing virus. Thus there is firm immunologic basis for crediting protection of the military to vaccination with older isolates.²⁷

Recent studies in children¹¹⁴ and adults²⁹ using vaccines of proper constitution and potency, and in sufficient dosage at appropriate intervals, have conclusively shown good antibody levels and clinical protection. One very important factor is the proper diagnosis of "flu." Without well controlled studies which include serologic and virus isolation surveys, influenza vaccination may be erroneously condemned. Parrott et al.¹⁰⁸ showed that influenza (1957-1958) as a cause of respiratory infections in hospitalized children accounted for only 5 per cent of cases whereas adenovirus accounted for 6 per cent, parainfluenza 16 per cent and respiratory syncytial virus 21 per cent. He and others^{74, 114, 133} have noted that influenza can be quite severe even when uncomplicated by bacterial infection. Since no specific therapy is available for flu, the advisability for routine vaccination becomes obvious, especially in high-risk groups. Also, in any given year it is not possible to predict the extent or severity of an epidemic.

When vaccination is given it must be done in an orderly fashion with repeated doses starting early in the fall. After the first injection, antibodies reach a maximum level during the second week.⁷ Studies²⁶ have shown the need for a second dose 2 weeks later for children¹¹⁴ and 1 to 2 months later for adults, which produces more sustained and higher antibody levels. The high-risk groups requiring routine annual influenza vaccination are (1) persons of all ages who suffer from chronic debilitating disease, especially cardiopulmonary, renal and metabolic disorders; (2) pregnant women; (3) persons over 45, especially over 65 years of age; (4) infants, especially between 3 and 12 months of age; (5) persons in critical services such as medical, health, public utilities, teaching, communication, military and specialized industry.

Absenteeism has been greatly reduced in industry by influenza vaccination.²⁸ Physicians should give serious consideration to the health of the community, and especially to pre-school children whose attack rate is the highest in time of epidemics.⁷⁴ It appears that general vaccination would be most effective in school children since this age group would undoubtedly decrease the incidence of flu among others.

The Armed Services are presently using the new 6-strain vaccine (1000 CCA [chick cell agglutination] units per ml.). This polyvalent vaccine contains:

Influenza Group A

400 CCA units Asian (A₂) strain (Jap 305)
 100 CCA units Swine strain
 100 CCA units PR-8 strain
 100 CCA units A₁/AA/57 strain

Influenza Group B

200 CCA units Great Lakes (1954) strain
 100 CCA units Lee (1940) strain

In years of anticipated epidemics it would be ideal for all groups to receive this new vaccine since the mortality rates are greatly increased in these years and death, often occurring after a total illness of only 3 days, is not necessarily related to bacterial complications.^{108, 114, 133}

With the new vaccines local reactions, soreness and swelling are common but rarely last 48 hours. Systemic reactions are rare except in children (20 per cent) who developed fever for 24 hours. Antipyretics should be used prophylactically. Our experience has shown that typhoid vaccine produces a higher reaction rate. The only contraindication to flu vaccination is known hypersensitivity to egg protein. See Table 5 for dose, intervals and route of inoculation.

The problem of duration of protection appears to be solved. Well controlled studies with adjuvant influenza³⁰ (and adenovirus⁹³) vaccines have shown a very low reaction rate, high and persistent (3 years) antibody titers, and a protection ratio for Asian flu of 94 per cent with a dose of 0.25 ml. These findings show the mineral oil-arlaclel adjuvant vaccines in small doses to be superior to the aqueous types. It is anticipated that these will be available next year. The addition of adenovirus to these vaccines further enhances their value to adults. The durable protection afforded will avoid the necessity of annual revaccination and make them more acceptable to the physician and his patients.

Table 5. Immunization Against Influenza

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Influenza vaccine, polyvalent (6-strain) A and B; 1000 CCA units per 1 ml. A killed suspension A and B influenza virus cultured in embryonated eggs. Vial 30 ml. Potency period 18 mos. stored 35.6° to 50° F. (2° to 10° C.).	High-risk groups. 1. Chronic debilitating dis. 2. Pregnant women. 3. Over age 45 yrs. 4. Age 3-12 months. 5. Personnel in critical services: medical, health, public utilities, education, communication, industry, military. 6. Institutionalized persons.	1 ml. × 2 SC at 1 to 2 mo. intervals prior to 1 Oct. Intradermal route <i>not recommended</i> . For children see Table 8. When adjuvant vaccine is available, 0.25 ml. × 2 IM.	Twelve months for aqueous vaccine. Three years for adjuvant vaccine
REQUIRED REPEAT INOCULATIONS			COMMENTS
<i>Booster:</i> 1.0 ml. SC of aqueous vaccine annually prior to 1 Oct. <i>Emergency dose:</i> 1.0 ml. SC. Epidemics may move slowly and appear late in winter. A single dose is better than none.	Do not freeze vaccine. If a person can eat eggs without allergic reaction, he can be vaccinated safely. In presence of strong allergic history or reactions to other vaccines, skin test: 0.1 ml. of vaccine, endermally (ED).		

Measles

During the past 50 years the mortality of most of the infectious diseases has fallen with the exception of hepatitis and certain of the encephalitides. Morbidity rates have also decreased although to a lesser degree. But measles shows a striking exception to these trends. During the last 10 years the notification rates have varied between a low of 406,162 in 1959 to a high of 763,094 in 1958.¹⁰² Almost 424,000 cases were reported in 1961 with approximately 400 deaths. These figures are undoubtedly lower than the true incidence since many cases are not reported and deaths may be attributed to the secondary complications rather than the primary disease. During 1955 in Mexico over 10,000 children, four-fifths of whom were under 5 years of age, were reported²⁴ to have died from measles or a complicating pneumonia. Countries such as Nigeria, Colombia, Greenland and India have reported a high incidence of deaths due to the effect of measles or its complications on underlying diseases such as tuberculosis, kwashiorkor or protein deficiency states. These factors have been discussed by Katz⁸¹ in his excellent review on rubeola.

Since measles is a universal disease, always present in pandemic form and has an attack rate (95 to 100 per cent) higher than any other infectious disease, it would be impossible to inactivate it or to interfere with its transmission. Therefore, one must strongly consider the use of active immunization to increase resistance of contacts. What should vaccination accomplish? It should not cause a reaction greater than the disease itself. It should reduce morbidity and mortality (5 to 25 per cent) in certain epidemics. It should reduce bacterial complications (5 to 15 per cent) such as otitis media and pneumonia, and viral complications such as croup, bronchiolitis and giant cell pneumonia. The most important reason to use the vaccine would be to avoid encephalomyelitis. The incidence approximates 1 in 1000 cases with permanent brain damage occurring in 75 per cent of patients.

In the past 5 years numerous clinical studies^{57, 77, 80, 135} with live (Enders) and killed measles vaccines (Edmonston strain) have provided sufficient experience (over 500,000 doses) to indicate that the vaccines are safe and effective. Measles vaccine appears to be acceptable because of the following properties:

1. *Ease of Administration.* The live vaccine is given one time, 0.5 ml. subcutaneously with or without gamma globulin (0.01 ml. or 40 measles neutralizing units/lb.) in a separate arm. The killed vaccine is given in 3 doses, 0.5 or 1 ml. each at monthly intervals or in 2 doses followed by 1 dose of live vaccine 1 month later.

2. *Reactions.* No severe local or immediate reactions have occurred with live vaccine. Between 20 and 70 per cent of vaccinees receiving live virus vaccine have had fever (102° F. average), and 5 to 40 per cent have had a rash of 48 hours' duration occurring 1 week after inoculation. The addition of gamma globulin reduces the incidence of fever (101° F. average) to 20 per cent and rash to 5 to 10 per cent. Less than 5 per cent of vaccinees who received 2 doses of killed vaccine plus live vaccine (KKL) developed systemic reactions. Local reactions occurred in 20 per cent of vaccinees receiving KKL or 3 doses of killed vaccines (KKK), and in several patients nodules occurred which subse-

quently drained nonpurulent material.⁵⁷ Fever (less than 102° F.) occurred in 10 per cent of recipients of killed vaccine and lasted about 24 hours. There have been no bacterial infections or evidence of central nervous system complications following over 500,000 immunizations with live vaccine B.

3. *Absence of Communicability.* There has been no spread of the virus from vaccinated children to their contacts⁸¹ nor have susceptible contacts acquired overt or inapparent infections as shown by clinical and serological studies.

4. *Serologic Response.* Live virus will produce serum antibodies against measles in 95 to 97 per cent of the vaccinees within a 2 to 3 week period. Administration of gamma globulin (0.01 ml./lb.) produces little difference in antibody production. Over a 4 year period these antibodies have remained quantitatively and qualitatively indistinguishable from those detected in children after natural measles.⁸¹ Both KKK and KKL vaccinee groups showed 90 per cent conversion rates.⁵⁷ Studies have shown that antibodies may no longer be detectable 3 to 8 months after immunization with killed virus vaccine.¹⁹ In addition, significant antibody titers do not occur for 2 to 4 months after the first dose of the killed vaccines. Since the live virus produces protection within the incubation period of natural measles it may prove valuable in aborting an epidemic, particularly, if an attenuating dose of gamma globulin is given at the same time.

5. *Prophylactic Efficacy.* Field trials⁸¹ have shown the protective value (100 per cent) in immunized children exposed to measles within 2 to 3 years after the live vaccine. Studies with killed vaccines have also shown good protection (65 per cent), but if only those cases noted 14 or more days after the third dose (KKK) were included then 96 per cent protection occurred.¹⁵² Further observations are in progress with the killed and further attenuated (77 passage) live vaccines.^{57, 135}

Leukemia is a definite contraindication to live measles vaccine. It should not be administered to a child with an acute febrile illness. Since the vaccine is cultured on chick embryo cells, known sensitivity to eggs should caution one to use antihistamines at the time of inoculation. Maternal antibodies in the infant under 6 months of age will inhibit

Table 6. Immunization Against Measles

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Measles, live (Enders) vaccine (Edmonston strain) grown on chick embryo tissue. Store at 5° C. (41° F.) or below.	All children over 8 months of age, institutionalized patients, those with debilitating disease and nonimmune pregnant women.	Live vaccine: 0.5 ml.* SC, one dose. Use within 8 hours of reconstitution. Killed vaccine: 0.5 ml.* IM \times 3 at monthly intervals or \times 2 then 4 weeks later live vaccine 0.5 ml.* \times 1 dose.	Live vaccine over 5 years, probably indefinitely if given after 8 months of age.
Measles, killed, alum-pptd., formalin—inactivated. Store at 4° C. (42° F.).	Use killed vaccine during pregnancy.		Unknown for killed vaccine.
REQUIRED REPEAT INOCULATIONS			COMMENTS
<i>Live vaccine:</i> Probably none. Booster may be necessary if first dose given between 6 and 8 months of age or within 6 weeks of gamma globulin injection. <i>Killed vaccine:</i> unknown.			Measles immune globulin: 0.01 ml./lb. may be given in separate arm concurrently with live vaccine. Contraindicated in patients with leukemia, on steroids, severe febrile illness, or hypersensitivity to egg or chicken.

* Follow manufacturer's directions regarding volume of dose.

antibody production by the live but not the killed vaccine.¹⁹ If gamma globulin has been given 6 weeks prior to inoculation, antibody production will be poor. Table 6 outlines inoculation schedules and procedures.

Pediatric Aspects of Immunization

The trend toward the use of multiple antigens and toward immunization at earlier ages reported⁸⁸ previously is now well established. The effectiveness^{2, 6, 17} of the alum-precipitated or aluminum hydroxide absorbed antigens has been adequately demonstrated by the marked reduction in incidence and mortality rates for the common contagious diseases. The immune response attainable in early infancy is such that combined D.P.T. toxoid is routinely started at the time of the first well baby examination at 4 to 8 weeks of age.^{1, 7} The recommended schedule is noted in Table 7.

With the use of depot antigens, higher titers result when inoculations are given at 1 to 3 month intervals. If only 2 injections are given even if 6 months apart, excellent diphtheria and tetanus antitoxin titers will be attained,^{41, 132} but a third injection must be given to attain adequate pertussis antibody levels. Using D.P.T. toxoid for the third injection

Table 7. Pediatric Immunization Schedule

IMMUNIZING AGENT	NO. DOSES, BASIC SERIES	INTERVAL, ROUTE AND QUANTITY OF EACH DOSE		
		1 mo. to 5 mos.	6 mos. to 5 yrs.	6 to 9 yrs.
Diphtheria and tetanus toxoids and pertussis vaccine, absorbed (D.P.T.) U.S.P.	4	0.5 ml. deep IM. First 3 doses 1 to 3 mos. apart. Fourth dose 8 to 12 mos. later.	0.5 ml. deep IM at same intervals as 1 to 5 mos. age. Follow injec- tion with 0.1- 0.2 ml. air.	Not recommended. Use diphtheria- tetanus toxoid combined (Pediat- ric) in same dose and schedule.
Smallpox vaccine, U.S.P.	1	See Table 1. Give at time of 2nd or 3rd D.P.T. or before overseas travel.	See Table 1. Re- vaccinate at time of 3rd D.P.T. if primary reaction did not occur.	See Table 1. Read result on 7th to 9th day and revac- cinate if required.
Poliomyelitis vaccine, oral, attenuated (Sabin) types 1, 2 and 3.	4	Two drops orally at 1 to 2 mos. intervals. Type 1 first, then type 3 and type 2 last. Trivalent vac- cine 1 to 3 (or more) months later.	Same as 1-5 mos. Types 2 and 3 may be given together but one dose of trivalent vaccine must be given 2 months later.	Same as 1 mo. to 5 years. Not less than 24 days be- tween doses.
BOOSTER DOSES		COMMENTS		
1. D.P.T. 0.5 ml. at 12 to 18 months age then 0.25 ml. at 4 to 5 years age.		Tetanus-diphtheria toxoids (adult use) should not be used to immunize children. May be used for a booster in children over 6 years who have been properly immunized as above. This preparation may be used in place of Schick test.		
2. Tetanus-diphtheria toxoid (for adult use) 0.1 ml. quadrennially and 0.5 ml. at time of injury.		Give 0.5 ml. fluid pertussis vaccine at time of pertussis exposure.		
3. Smallpox—revaccinate quadrennially (every 4 years).		Give 0.5 ml. diphtheria-tetanus toxoid (Pediatric) combined for child under 10 yrs. of age at time of diphtheria exposure. See Table 6 for measles vaccine.		
4. Poliomyelitis, oral—unknown.				

will increase the titers by a hundredfold. Boosters given 6 to 12 months later will maintain these highly protective levels. If the third dose of a series is missed, i.e., not given within a 3 to 6 month interval, it is *not* necessary to "restart" a series of immunizations. After the first booster (fourth injection) of 0.5 ml. is given, subsequent doses may be reduced to 0.25 ml. These are given at 3 to 4 year intervals. In an epidemic situation or after direct exposure, booster doses of pertussis or diphtheria are advisable. At the time of an injury, however minor, tetanus toxoid must be given unless the last booster was given during the previous 12 months. An ideal time for D.P.T. and typhoid boosters would be just prior to a camping or overseas trip.

In this connection we and others⁵⁸ have been amazed at the opposition, apathy and occasionally fear of vaccination which some parents have shown. Recent surveys^{67, 97} have revealed that in spite of the availability of free vaccines the vaccination rates were low. Certainly we agree with Meyer and Haggerty⁹⁷ that such procedures should be carried out on a family-wide basis with the parents receiving their vaccines at the same time as their children.

There are few contraindications to immunization in children but certain precautions are necessary in order to preserve a good record of almost complete freedom from complications.

PRECAUTIONS. 1. Careful sterilization of equipment and cleansing of skin with 70 per cent alcohol or 2 per cent tincture of iodine.

2. Inject depot antigens deep intramuscularly and follow with 0.1 to 0.2 ml. of air. Give all injections in the midanterolateral thigh of infants and young children⁶⁵ to avoid sciatic nerve injury.

3. Antigens without adjuvants (fluid or plain vaccines) may be given intra-cutaneously or subcutaneously.

4. Always rotate injection sites.

5. Immunize only well infants. If a child has an allergic rhinitis or is in the convalescent afebrile phase of a mild respiratory infection the inoculation may be given.

6. Acetylsalicylic acid, 65 mg. per year of age, may be given 2 to 4 hours after injection, especially if a previous inoculation produced fever.

7. Always question regarding a past history of febrile convulsions or the occurrence of fever, somnolence or unusual reaction following a previous injection. If any of these have occurred then the volume of the next injection should be reduced to 0.05 or 0.1 ml. If a severe reaction such as a convulsion or allergic rash occurred, single antigens only should be given in small fractional doses at weekly intervals. Aspirin in combination with phenobarbital, 30 mg. per year of age up to a total of 120 mg. may be given 2 to 4 hours after injection and repeated in 4 hours as indicated.

8. Patients receiving steroids should have active immunization deferred since optimal antibody response is not attained.

CONTRAINDICATIONS. 1. Active infection or fever (over 101° F.). Final immunity will be excellent even if intervals between injections are prolonged up to 6 months.

2. Cerebral dysfunction in an infant should delay immunization until after 1 year of age. Fractional doses of single antigens should be employed.

3. During an outbreak of poliomyelitis one should defer inoculations or use fluid vaccines instead of the depot type in infants over 6 months of age who

have not been immunized against poliomyelitis. Paralysis may occur in the extremity injected with the depot vaccine.

4. Smallpox vaccination in an eczematous child or the siblings of an eczematous child. In children with impetigo or generalized dermatitis, vaccination should be deferred until the skin is clear. A mild nonspecific diaper rash should not delay smallpox vaccination. The allergic child should receive all other immunizations in a routine manner.

Reactions to D.P.T. toxoid are infrequent and rarely severe when the above precautions are followed. Our experience compares to others⁷ with only 10 sterile abscesses in over 15,000 combined toxoid (depot) injections. Only one of these drained spontaneously and none was incised. Fever (over 101° F.) occurred in a small percentage of patients. The fever rarely continues beyond 12 hours.

Immunization against typhoid fever is not recommended as part of a routine program in infants and children, but should be carried out in all cases where an epidemic exists or the child lives in or is moving to an endemic area. The indications for influenza vaccine are discussed in that section; however, many pediatricians and most epidemiologists are recommending influenza vaccine for all young infants as well as children with chronic diseases. The dose is noted on Table 8. Measles vaccine should be given to all susceptible children (see Table 6).

With increased world travel, children often accompany their parents

Table 8. Special Pediatric Schedule

IMMUNIZING AGENT	NO. DOSES, BASIC SERIES	INTERVAL, ROUTE AND QUANTITY OF EACH DOSE		
		1 mo. to 5 mos.	6 mos. to 5 yrs.	6 to 9 yrs.
Typhoid-paratyphoid vaccine U.S.P.	2	0.1 ml. SC or IM at 4 week intervals. Booster: 0.1 ml. endermally every 1-3 years.	0.2 ml. SC or IM at 4 week intervals. Booster: 0.1 ml. endermally every 1-3 years.	0.3 ml. SC or IM at 4 week intervals. Booster: 0.1 ml. endermally every 1-3 years.
Influenza vaccine, poly- valent A, B, 1000 CCA units per ml.	2 or 3	0.1 ml. SC \times 3. Two weeks between 1st and 2nd doses. Two mos. between 1st and last.	0.2 ml. SC \times 3. Same interval as 1 to 5 mos. Table 5.	0.5 ml. SC \times 2 at two month inter- vals. Booster: Same as initial dose of each series.
Measles—Enders B (Edmonston strain) live vaccine.	1	Not given.	0.5 ml. SC. Booster: unknown.	0.5 ml. SC. Booster: unknown.
Typhus vaccine U.S.P., epidemic.	2	Not given.	0.1 ml. SC then 0.3 ml. in 4 weeks. Booster: 0.1 ml. annually in en- demic areas, rou- tinely every 5 yrs.	0.3 ml. SC then 0.5 ml. 4 weeks later. Booster: same as initial dose of each series.
Cholera or plague vac- cine U.S.P.	2	Not given.	0.1 ml. SC, then 0.3 ml. 4 weeks later. Booster: 0.3 ml. every 6 months in endemic areas, rou- tinely every 3 yrs.	0.3 ml. SC, then 0.5 ml. 4 weeks later. Booster: 0.5 ml. every 6 months in endemic areas, rou- tinely every 3 yrs.
Yellow fever vaccine, U.S.P.	1	Not given unless ar- riving in India from infected area.	0.5 ml. SC. Booster: 0.5 ml. every 6 years.	Same as 6 mos. to 5 years age.

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overseas. They necessarily require the same immunizations, therefore the dosages³ of cholera, plague, typhus and yellow fever are included in Table 8.

GROUP II. IMMUNIZATION PROCEDURES WHICH ARE MANDATORY UNDER CERTAIN CIRCUMSTANCES

There are several diseases for which immunization procedures are available but will be required only for those who travel to countries where such diseases are endemic or which are demanded by the country before admission is granted. Rabies immunization obviously must be included since the bite of a rabid animal makes specific immunization imperative. Typhoid immunization, routinely given to military personnel but not their dependents unless traveling to or residing in areas outside the 50 United States, ideally should be an integral part of all civil defense programs. As the vaccine's antigenicity is improved and its reaction rate reduced (probably by eliminating paratyphoid A and B), it will resume its former status as a routine immunization procedure.

The immunizations required by various countries tend to follow continental divisions. Rather than employ tables³⁸ which list each country's requirements we have included a World Immunization Map utilized by the Armed Services (Fig. 1).^{*} The map was prepared essentially for the traveler who leaves the United States. The routine (R areas) immunizations noted in the legend of the map for military personnel are not mandatory for civilians. However, the basic requirements for travel to all countries outside the 50 United States and Canada are smallpox, tetanus-diphtheria, typhoid and oral polio. Several countries (e.g., India—yellow fever) demand immunization against diseases which are not present in their country in attempts to prevent such disease from gaining a foothold. The Scandinavian countries do not require typhus, even though they are located in a T area, but since many Eastern European countries do and the traveler destined for Sweden may pass through one of these, it would be appropriate to obtain typhus inoculations. Typhus is also recommended for Mexico and the Andean region of South America. Thus the immunization map should serve as a rough guide only.

The Public Health Service of the U.S. Department of Health, Education and Welfare publishes a booklet of Immunization Information for International Travel. Each year the booklet is revised inasmuch as various countries change their requirements from time to time. Thus the prospective traveler is advised to obtain the latest information from the nearest Public Health Service office. As noted on the world map, the Armed Services have now included influenza, typhus and yellow fever as part of the "routine" inoculations for military personnel. Military dependents presently do not receive typhoid, cholera, typhus, yellow fever or influenza vaccines unless required for the geographical area visited or as indicated by their own health needs (e.g., influenza [Table 5]). Influenza immunization will undoubtedly become a routine procedure when the adjuvant preparation becomes available. All of the immunization procedures except for yellow fever can be performed by one's private physician. The latter

* Courtesy Armed Forces Institute of Pathology and A.F.E.B.



Fig. 1. World Immunization Map used by U.S. Armed Forces. (See text for discussion.)

can be obtained at one of many centers designated to perform this inoculation.

Prior to departure the traveler should obtain an International Certificate of Vaccination, PHS-731, and have all immunization procedures accomplished entered thereon by his physician. Additional space in the new edition permits entries regarding the travelers personal health history. This certificate, approved

by the World Health Organization, is obtainable from the Superintendent of Documents, Government Printing Office, Washington, 25, D.C., or from any of the Public Health Service offices for tourists. The charge is 10 cents.

Typhoid and Paratyphoid Fever

In the past decade the incidence of typhoid fever in the United States has decreased more than 50 per cent with only 816 cases in 1960 and 814 in 1961. A high incidence continues in Europe in contrast to Great Britain. Most public health authorities credit this decrease to improved sanitation rather than to the effectiveness of typhoid vaccine. The most recent controlled field trial²⁵ in Yugoslavia indicated 65 per cent protection with the heat-killed phenol-preserved vaccine. In addition the alcohol killed vaccine appeared to be ineffective, and Vi antigen did not appear to be of major value as an immunizing agent.

In a recent report⁴⁷ 62 cases of typhoid fever occurred among 408 persons in Germany, all previously immunized except 1 child who reacted no more severely to the disease. Only 2 of 52 members of the Armed Forces contracted the disease. One might attribute this lower incidence to more frequent and recent reimmunization of the service man, but marked differences in the dose of bacilli ingested and previous natural immunity of the group must be considered.⁴¹ There is little evidence regarding the efficacy of paratyphoid vaccine; moreover much of the unpleasant reaction to T.A.B. vaccine is due to the paratyphoid B component.⁴⁸

In spite of doubts about the value of typhoid vaccine expressed in our previous review,⁸⁸ the vaccine obviously has been moderately effective against typhoid fever during the past half century. In an excellent survey of this problem a warning was given by Means⁹² emphasizing the fact that proper application of public health measures could eradicate

Table 9. Immunization Against Typhoid and Paratyphoid Fevers

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Typhoid-paratyphoid vaccine U.S.P. Triple vaccine containing 1000 million <i>S. typhi</i> and 250 million each of <i>S. schottmüller</i> and <i>S. paratyphi</i> organisms per ml. Vial 50 ml. Heat-killed in 0.5% phenol. Stored at 35.6° to 50° F. (2° to 10° C.). Potency period 18 months.	All persons living in or traveling to areas of questionable sanitary standards or where the disease is endemic. Emergency situations, e.g., floods. Military personnel, physicians, nurses, food handlers and contacts of typhoid patients or carriers.	Standard course, 2 inoculations subcutaneously of 0.5 ml. each at not less than 4 week intervals. For children refer to Pediatric Schedule, Table 8.	Indefinite but at least 1 year. Anamnestic response to booster dose probably satisfactory even if several years have elapsed since basic series.
REQUIRED REPEAT INOCULATIONS			COMMENTS
All persons living in areas described above should receive annual booster of 0.1 ml. endermally (ED) or 0.5 ml. SC. Others should be given booster 0.1 ml. ED quadrennially. Vaccine contraindicated: 1. Acute febrile illness. 2. Active tuberculosis.			Local and systemic reactions are common, but not serious. Reactions are less frequently encountered when the inoculations are given ED (not recommended for basic series). If reactions are severe, subsequent doses should be reduced and antipyretics administered.

the disease. The vaccine is certainly advocated in areas where the disease is endemic, and for those who travel through these areas or where sanitation facilities are poor such as rural camps, resorts, and at times of disaster, as floods. Military personnel, physicians, nurses, food and dairy workers and those living under field conditions should be immunized. Proper sanitary measures related to food, water and waste disposal as well as the identification of cases and carriers still constitute the major means of preventing typhoid fever.

Contraindications to the vaccine are few. It should not be given to persons with active tuberculosis, an acute febrile disease or those receiving steroids. When practicable the vaccine should not be given with another fever-producing vaccine such as typhus or cholera nor just prior to intensive physical activity during hot weather. About 75 per cent of individuals have some local reaction² while 25 to 50 per cent have systemic (grippe) reactions lasting 24 to 36 hours. These are readily alleviated by acetylsalicylic acid, 65 mg. per year of age up to 324 mg. total, given every 4 hours. Since the second or third (booster) injection may result in a more severe reaction, antipyretics should be started 3 to 4 hours after the injection. If a severe reaction does occur, the subsequent dose should be halved. The resultant immunity will be enhanced, not decreased, by dividing the total (basic) dose into more than 2 or 3 injections. Administration of the recall or booster dose using 0.1 ml. endermally rather than 0.5 ml. subcutaneously will produce a good antibody response and greatly lessen the severity of the reaction. The basic series^{2, 43} consists of two 0.5 ml. doses subcutaneously followed by two reimmunizing doses at 4 year intervals for persons remaining in the 50 United States and Canada.

Typhus Fever

Typhus vaccine is recommended only to those whose travels take them into zones where epidemic or classic Old World typhus exists. The vaccine is a killed suspension of *Rickettsia prowazekii* cultured by the Cox embryonic chick yolk sac method. Since this is a highly effective immunizing procedure,^{2, 106} the dose has been reduced to 2 injections of 0.5 ml. each at 4 week intervals. The immunity lasts about 12 months, with a peak period of immunity reached 3 months after inoculation. Gould and Goodner⁶⁹ and Murray et al.¹⁰⁶ have demonstrated that single booster injections elicit satisfactory antibody response even if given as late as 6 years after the basic series. Booster doses are given where typhus hazard exists annually and also in the presence of an epidemic.

Fox⁵⁴ and others⁵⁵ have published an account of their work with an avirulent strain of *Rickettsia prowazekii* (Strain E) for use as a living agent to immunize man against epidemic typhus. It has been shown to have some protection against murine typhus in laboratory workers.¹⁵³ It is claimed that in comparison to a primary course of the Cox vaccine it produces a superior immunity as measured by uniformity of response and by both effectiveness and duration (3 years). It is accompanied, however, by frequent systemic reactions.

Table 10. Immunization Against Epidemic Typhus Fever

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Typhus vaccine U.S.P. epidemic—a suspension of killed <i>Ri: ketsia prowazekii</i> cultured by the Cox yolk sac method. Vial 20 ml. Potency period 18 months stored at 35.6° to 50° F. (2° to 10° C.).	All individuals residing in or traveling to areas where epidemic typhus exists. See World Map (Fig. 1).	Two subcutaneous injections of 0.5 ml. each at intervals of not less than 4 wks. For children see Table 8.	Immunity is good for 1 year, and probably persists several years.
REQUIRED REPEAT INOCULATIONS			COMMENTS
<i>Booster dose:</i> 0.5 ml. subcutaneously shall be given once each year where typhus hazard exists, with additional doses whenever any unusual threat of outbreak appears. Satisfactory recall can be obtained 5 years after basic series.			Severe reactions are uncommon. This vaccine does not protect against murine, endemic typhus transmitted by the rat flea, nor against "scrub typhus" transmitted by mites. Allergy to egg and chicken protein constitutes only contraindication.

Very few severe reactions have been reported. Allergy to egg or chicken protein constitutes the only but very strong contraindication. Wright¹⁵⁵ in 1959 reported a near fatal case of anaphylaxis due to the injection of typhus vaccine and found 12 similar cases in the literature, 2 of which terminated fatally. Table 10 outlines immunizing procedures.

Cholera

While cholera has not occurred in the Americas since 1911 it still remains a serious problem in Asia. During 1961, almost 50,000 cases with 17,541 deaths were reported worldwide, the majority occurring in India and East Pakistan. *Vibrio comma* which causes Asiatic cholera has been shown to possess 3 antigenic factors.¹¹⁶ One of these is an endotoxic lipid which injures intestinal epithelium, so that it permits free escape of fluids and electrolytes. Another endotoxin causes flaking of the epithelium by a mucinase action, which alters the permeability of the bowel wall permitting absorption of toxic substances as well as leading to flake formation which gives the diagnostic rice-water appearance to the stools. It has been suggested⁸⁹ that the addition of cholera mucinase to the fluid vaccine would enhance the protective value of this immunizing agent against cholera infection. However, it is not being used at the present time. Immunity supposedly stimulated by the current vaccine renders intestinal epithelium resistive to effects of endotoxins.

No clear-cut satisfactory field trial has ever been made of cholera vaccine,⁴¹ but the marked difference in the incidence of the disease between unvaccinated groups as compared to vaccinated in large studies suggest it has its place in the protection against the disease. Reliance must not be placed exclusively on it since improvement in sanitation is the more important factor. It is recommended for all individuals traveling to or through areas where the disease is endemic or whenever an epidemic occurs. Table 11 outlines immunizing procedures.

Table 11. Immunization Against Cholera

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Cholera vaccine U.S.P. A suspension of 8000 million killed <i>Vibrio comma</i> per ml. Vial 20 ml. Potency period, 18 months stored 35.6° to 50° F. (2° to 10° C.).	All individuals traveling to or through areas where there is danger of endemic or epidemic cholera. See World Map (Fig. 1).	Two SC or IM injections 4 weeks apart. First 0.5 ml., the second 1 ml. For children see Table 8.	Immunity is probably relative and lasts for only 6 to 12 months.
REQUIRED REPEAT INOCULATIONS			COMMENTS
<i>Routine booster:</i> 0.5 ml. to be given subcutaneously every 6 months as long as there is danger of infection by cholera. Recall dose is effective if given within 4 years of basic series or last stimulating dose.			No severe reactions have been reported. International Quarantine Commission accepts cholera immunization as effective 6 days after the first injection.

Rabies

There are few circumstances which pose more difficult decisions than those presented by individuals who have been bitten by animals that may or may not be rabid. Although dogs are the most frequent animals involved, rabies may occur in other carnivores such as foxes, wolves, coyotes and jackals who may transmit the disease to cattle and sheep. Bats may harbor the virus for months in contradistinction to other animals who die of the disease within 10 to 40 days. The significance of this is emphasized in a recent report²¹ suggesting inhalation as another route for the transmission of rabies.

Hydrophobia, although a rare disease, is one from which there has been no authenticated recovery in an untreated person. This statement may have to be modified in the light of the report by Rizzolo and Osborne.¹²⁰ They cited Dr. Relova's report in Santo Tomas which described several purported cases of recovery from rabies in man. There is also a possibility that subclinical infections may occur since Ruegsegger et al.¹²⁷ disclosed that 6 per cent of a study group (with no previous history of rabies vaccination or an antecedent contact with rabies virus) had neutralizing antibodies to rabies.

The saliva of the rabid animal contains the virus, and the duration of the incubation stage varies more with the amount of infecting saliva introduced than with the anatomical site. Thus, multiple bites on the body or extremities may have a shorter incubation period (10 days) than single bites on the head or face, but inasmuch as the virus travels along nerve pathways to reach the central nervous system, face, head and neck bites are usually considered graver emergencies than torso and extremity injury.

Despite repeated exhortations, people will prematurely kill and dispose of the biting animal, and the clinician must use the finest judgment in deciding whether or not to subject the patient to the unpleasant series of vaccine injections. Consultation with the local health officer is always advisable in such instances.⁵⁰

When a patient is bitten by a dog the physician should have measures taken to isolate the dog and keep him under observation for 10 days. Should the dog die before then or show symptoms of rabies by that time he should be killed and the brain tissue examined for Negri bodies using the fluorescent antibody technique⁵⁰ in addition to the standard microscopic methods. The absence of Negri bodies in the brain does not preclude the advisability of antirabies immunization.

While the past few years have seen no major breakthrough in the prevention of the development of rabies in man following exposure, there has been appreciable progress in several aspects of this vital problem. Active immunization of high-risk groups such as mail carriers, veterinarians or speleologists has been outlined by Tierkel.¹⁴⁶ Three endermal inoculations of 0.2 ml. duck embryo vaccine are given at weekly intervals followed by a booster of 0.2 ml. endermally 2 to 6 months later. Since all vaccinated individuals do not respond readily with detectable antibodies, booster doses should be repeated until antibody is detected. Subsequent boosters are given routinely at 2 year intervals or at the time of a bite.⁵⁰ In a limited trial Ruegsegger and Sharpless,¹²⁸ using HEP Flury (live) rabies vaccine with aluminum hydroxide adjuvant, found a prolonged antigenic stimulus and immunized 95 per cent of the subjects. The possibilities of using this vaccine for postexposure protection should be studied. During the past 8 years the Flury vaccine has produced a high grade of immunity in dogs.

The postexposure prophylaxis of rabies, however, still leaves much to be desired. Successful immunization is based upon the classic work of Pasteur in which, by daily injections of killed fixed virus, sufficient active immunity is produced during the prolonged incubation state of the disease (15 to 200 days) to prevent actual clinical expression. The following summary together with the accompanying Table 12 covers the important features involved in handling human exposure to rabies. Careful consideration of the circumstances will assist in deciding whether or not to immunize a patient.

LOCAL TREATMENT. Kaplan et al.⁷⁹ advise that the wound be swabbed and flushed vigorously with soap or detergent after infiltrating the tissue proximal to the wound with procaine to minimize the pain. The wound itself should be infiltrated with hyperimmune serum where indicated. Cauterization is not recommended by most authorities.

SPECIFIC POSTEXPOSURE PROPHYLAXIS OF RABIES. When indicated, hyperimmune antirabies serum (0.5 ml. or 40 I.U. per kg./body weight) should be administered within 24 hours if possible and preferably within the first 72 hours following exposure after proper precautions have been taken to rule out sensitivity to horse serum. Some authorities¹²⁰ feel that it should still be administered even if 72 hours have passed. The fourth report of the WHO Expert Committee on Rabies⁵⁰ recommended the addition of two extra doses of vaccine at long intervals (10 and 20 days) after the standard course of either duck embryo or rabbit vaccine in persons who have also received antirabies hyperimmune serum. The serum slows the development of antibodies in response to the antirabies vaccine, therefore booster doses are necessary. Even though the serum

Table 12. Indications for Rabies Vaccine Prophylaxis and Specific Postexposure Treatment²

BITING ANIMAL*			
NATURE OF EXPOSURE	At Time of Exposure	During Observation Period to Ten Days	RECOMMENDED TREATMENT†
I. No lesions: Indirect contact or direct contact over 7 days	Rabid or healthy	Rabid or healthy	None
II. Licks: (1) Unabraded skin (2) Abraded skin, scratches and un- abraded or abraded mucosa	Rabid or healthy (a) Healthy (b) Signs suggestive of rabies (c) Rabid, escaped, killed or unknown	Rabid or healthy Clinical signs of rabies or proved rabid (laboratory) Healthy —	None Start vaccine at first signs of rabies in the biting animal. Start vaccine immediately; stop treatment if animal is normal on fifth day after exposure. Start vaccine immediately.
III. Bites: (1) Mild exposure	(a) Healthy (b) Signs suggestive of rabies (c) Rabid, escaped, killed or unknown (d) Wild (wolf, jackal, fox, bat, etc.)	Clinical signs of rabies or proved rabid (laboratory) Healthy — —	Start vaccine at first signs of rabies in the biting animal. Start vaccine immediately; stop treatment if animal is normal on fifth day after exposure. Start vaccine immediately. Serum‡ immediately, fol- lowed by a course of vac- cine unless circumstances change.
(2) Severe exposure (multiple, or face, head, finger or neck bites)	(a) Healthy (b) Signs suggestive of rabies (c) Rabid, escaped, killed or unknown; any wild animal (wolf, jackal, fox, bat)	Clinical signs of rabies or proved rabid (laboratory) Healthy —	Serum immediately; start vaccine at first sign of rabies in the biting animal. Serum immediately, fol- lowed by vaccine; vaccine may be stopped if animal is normal on fifth day after exposure. Serum immediately, fol- lowed by vaccine. Give full course (14 days) un- less circumstances dictate otherwise.

* This schedule applies equally whether or not the biting animal has been previously vaccinated.

† Under certain special conditions treatment may be modified. For example, in rabies-free areas, as eastern Massachusetts, no specific therapy may be needed; however, the biting animal should be observed for 2 weeks.

‡ Dose of antiserum: 1000 units per 18 kg. (40 pounds) body weight. If more than 24 hours elapses or the wound is about the head and neck, the dose should be increased 2 or 3 fold.

is purified and concentrated it may produce adverse reactions in about 20 per cent of the recipients. In known allergic individuals concurrent administration of antihistamines may reduce the incidence and severity of reactions.

The duck embryo vaccine has now replaced the rabbit vaccine in the hands of most workers.⁴¹ Protective antibodies occur between the eleventh and fifteenth days, and within one month of the first injection 95 per

cent of individuals will have measurable antibodies.⁷¹ The full course consists of 14 subcutaneous injections, the same as the rabbit vaccine, of 1 ml. each into alternate sides of the abdominal wall. Local reactions (20 per cent) are mild consisting of redness and induration usually at the site of previous injections. These occur about the sixth to the tenth day. Regional lymphadenopathy may occur. Caution should be used in administering the vaccine to persons with allergy, particularly to eggs. Systemic reactions are less common (4 per cent) consisting of fever, malaise or drowsiness. The occurrence of central nervous system symptoms would preclude further injections. One case of transverse myelitis with complete recovery has been reported.¹⁰³ Neuroparalytic complications (1 in 3000) are one of the chief disadvantages of the rabbit nervous tissue vaccine. Gibbs et al.⁶⁴ demonstrated electroencephalographic abnormalities in an appreciable number of those who were given the rabbit vaccine, but not in the series of persons immunized with duck embryo vaccine.

In areas where rabies is prevalent among the animal population and human exposure is frequent, the vaccine has proved to be very effective in rabies prophylaxis.¹²⁰ Of more than 40,000 trials with this vaccine there are only 5 reported failures,⁴⁶ which is a great improvement over Semple vaccine (3 per cent failures). Dean and Sherman³¹ have questioned the potency of lots of duck embryo vaccine; however, the potency has recently been increased. If re-exposure occurs in persons who have previously received the first course of vaccine, no treatment is required if the interval is less than 3 months, but if between 3 and 6 months one reinforcing dose is given, and if over 6 months a full course of treatment is probably necessary.

Tetanus immunization with tetanus toxoid (or antitoxin) should be given in all cases of animal bites. Steroids¹⁶ probably should not be used in the treatment of side reactions to antirabies prophylaxis since they may interfere with antibody production.

Plague

Pasteurella pestis, the cause of plague, and the disease itself have been of considerable interest to immunologists.¹¹⁵ The organism is surrounded by a gelatinous envelope which contains an antigen that is necessary to produce efficient immunization for some species while a somatic antigen is required for others. Since the disease occurs in two forms (bubonic and pneumonic), studies continue to obtain a vaccine that will be as effective against the more severe respiratory form as it is against the bubonic.⁴³ Inactivated and live vaccines are in use. Although each has its adherents, the live vaccine is unstable when held in suspension longer than 2 weeks. Pollitzer¹¹² reviewed all aspects of plague including the merits of the two types of vaccine.

The prevalence of plague throughout the world at present is at a very low ebb. This is probably due to the natural periodicity¹¹² of the infection rather than any public health measures, and is therefore no cause for relaxation of vigilance. No scientifically controlled data⁴¹ on the efficacy of either type of the vaccine are available. However, observation on the use of both in large population groups substantiates the fact that they

Table 13. Immunization Against Plague

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Plague vaccine U.S.P. A suspension of 2000 million killed <i>Pasteurella pestis</i> per ml. Vial 20 ml.	All individuals residing in areas where serious danger from plague exists and in the presence of an epidemic only.	Two subcutaneous injections given not less than 4 weeks apart, the first consisting of 0.5 ml. and the second injection of 1 ml.	Partial protection for 4 to 6 months with present vaccine.
Potency period 18 months stored at 35° to 50° F. (2° to 10° C.).			
REQUIRED REPEAT INOCULATIONS			Comments
<i>Booster:</i> 0.5 ml. shall be administered every 4 to 6 months so long as plague hazard exists.			Local and systemic reactions are common but not serious with the killed vaccine.

are efficient in protection against the disease and the reduction of mortality. Public health measures toward the elimination of the natural reservoirs and vectors of plague will still continue to be the major factor in the control of the disease. In areas where sylvatic plague is endemic the vaccine will be an important method of reducing the danger of infection in exposed individuals. The advantages of periodic vaccination against plague in endemic areas was well demonstrated⁴¹ in the Malagasy Republic prior to the Second World War.

The Armed Forces^{2, 3} use a formalin-killed suspension of *P. pestis* which appears to give only partial protection.^{2, 96} Table 13 outlines immunization procedures.

Tuberculosis

The continued efficacy of B.C.G. vaccine has been shown in large scale trials during the past 20 years.⁴¹ Space prohibits a review of these studies, or of chemotherapy or chemoprophylaxis of tuberculosis which are discussed in detail by Raffel,¹¹⁷ Mount and Ferebee¹⁰⁵ and others.^{33, 142} The following well established aspects of B.C.G. vaccination are summarized:

1. B.C.G. (bacillus of Calmette and Guerin) vaccine is composed of avirulent human tubercle bacilli. It is quite safe since 200 million persons have been inoculated with only 1 case of progressive tuberculosis which occurred in a child in 1953.⁹⁵

2. Following inoculation about 99 per cent of vaccinees become tuberculin positive, and 82 per cent were still positive, after 8 years, to a single vaccination.^{123, 124}

3. It appears that the vaccine affords 75 to 80 per cent protection against clinical tuberculosis in tuberculin-negative individuals subject to a significant risk of infection. This resistance appears to be maintained for periods of 6 to 10 years.

4. The present vaccine, licensed in 1950, is freeze-dried, potent and well standardized.

5. It is simply administered by the multiple-puncture method of Rosenthal. If the tuberculin test is negative in 8 weeks, revaccination

is performed. Local reactions with the transcutaneous route are negligible, but following intracutaneous inoculation, 0.1 mg. of vaccine in 0.1 ml., local ulcers form in a high percentage of cases with abscesses and suppurating lymph nodes in a small percentage.

6. Contraindications to vaccination are a positive reaction to tuberculin, acute infectious disease, diseases of the skin, prematurity and marked debilitation.

7. Other immunizations except smallpox may be given at the same time provided different sites are employed.

The present methods of control of tuberculosis should continue to be applied to all segments of the population. Traditionally these include mass chest x-ray and tuberculin test case-findings, isolation of known cases, and treatment in addition to chemoprophylaxis with isoniazid. The incidence of tuberculosis in this country has decreased almost 50 per cent since 1950 while the death rate has fallen precipitously from 200 per 100,000 population in 1900 to 20 in 1950 and barely 6 in 1960. Tuberculosis has been practically eradicated as a cause of death among white persons age 1 to 24 years. The most important factors contributing to this are improved standards of living, high levels of health education and specific antibiotic therapy of tuberculosis. Thus in areas of low degree tuberculin sensitivity, B.C.G. vaccination will not be a primary part of the program. However, in some areas or countries of high prevalence and high degree tuberculin sensitivity, B.C.G. vaccination may be indicated during the first month of life with revaccination at school entry and during adolescence depending on the persistence of a positive tuberculin test.

It is now evident that certain select groups of nonreactors to P.P.D. or tuberculin may well benefit by B.C.G. inoculation. These persons or groups were recently delineated by the Tuberculosis Control Advisory Committee.¹¹³ Under circumstances in which exposure to tuberculosis infection cannot be avoided, risk of disease is high, and periodic examination and supervision of those exposed is a practical impossibility, the committee recommends the use of B.C.G. Where a patient with communicable tuberculosis cannot be isolated, as at home, and his contacts are not examined regularly, B.C.G. should be given. Another example for consideration is the tuberculin-negative contact of a tuberculosis patient in a group of migrant workers or in a highly mobile population group. Other groups to consider are certain selected medical or paramedical personnel who may be unduly exposed to tuberculous patients, or certain population groups or isolated communities (American Indians) where tuberculosis mortality and morbidity rates are high. If a hospital or institution has established an adequate tuberculosis control program, very little exposure to tuberculosis should occur. The committee emphasized that B.C.G. vaccination should not be considered as a substitute for other control measures. The newborn infant whose parents have tuberculosis should be inoculated when it is economically or otherwise impossible to separate them. Vaccination should be performed soon after birth.^{1, 147} An isoniazid-resistant B.C.G. vaccine has been developed and results of initial studies⁶⁰ in newborn infants appear promising. The infant is immunized with the vaccine and protected temporarily from his contact by concurrent isoniazid administration.

Certainly in this country most of the population does not require immunization; in fact, widespread B.C.G. vaccination is contraindicated because it eliminates the usefulness of the tuberculin test as an epidemiologic and diagnostic tool. In addition, institution of specific antituberculous chemotherapy may be inordinately delayed.

Yellow Fever

This immunization procedure is one of the most effective of all.^{24, 41} With it and the great advances made in the knowledge of the epidemiology of the disease since the turn of the century when the *Aedes aegypti* mosquito was established as the vector, one might expect the disease to be well in hand. Unfortunately, such is not the case and Yellow Jack or "Calenture"⁷⁸ still remains an important public health problem.

Spence¹⁴¹ and others have pointed out the difficulties in ascertaining whether yellow fever is actually present at any given time in an area where "conditions possible for the natural (monkey-haemagogus) cycle are known to exist." Since their experience in Trinidad has shown that the virus can remain present and active in an area for at least 6 years and that the number of monkeys in this region are not plentiful enough to keep it going on a year in year out basis involving the monkey cycle, these authors believe that other factors must play a part. This raises the question of how complete our present day knowledge of the disease is.

India, Pakistan and Ceylon have large areas where the basic factors for the successful establishment of yellow fever exist. These factors are sustained environmental high temperatures and the *Aedes aegypti* mosquito in abundance, but so far yellow fever virus has never gained admittance. These countries maintain a strict quarantine and constant vigil so that no one who has been in an endemic area may be admitted unless he has been immunized at least 12 days prior to arrival. If this virus ever gained a foothold in those countries, havoc would result because therapy of yellow fever in contrast to the efficacy of immunization is essentially futile.

Modern transportation has shortened the time required for journeys from southern Mexico and Central America to the United States. Jungle fever, the sylvatic variety of yellow fever, is endemic in Brazil and therefore, reintroduction of yellow fever to this country is possible. Although the last outbreak of yellow fever in the U.S. occurred almost 60 years ago it is an ever present danger in the yellow fever receptive areas (World Map, Fig. 1). It is not improbable that a case of yellow fever occurring in this country might present itself to the physician as typhoid, malaria, influenza or dengue unless he had a high index of suspicion. The severe form of the disease might be misdiagnosed as acute yellow atrophy, infectious hepatitis or leptospirosis. Persons 6 months of age or over must present a valid yellow fever vaccination certificate when arriving in or destined for yellow fever receptive areas of the United States or its possessions within 6 days of departure from infected areas.¹⁵

Immunization against yellow fever (Table 14) is accomplished by a single inoculation of 0.5 ml. of a freshly prepared 1:10 suspension of lyophilized egg yolk vaccine (17D strain). Any solution over 1 hour old is discarded. Allergy to egg or chicken protein constitutes the main contraindication. Postvaccination reactions are seldom severe. Slight redness may appear at the site of injection, and 5 to 8 days after inoculation 5 to 10 per cent of persons may develop malaise, headache, back-

Table 14. Immunization Against Yellow Fever

IMMUNIZING AGENT	RECOMMENDED FOR	METHOD OF ADMINISTRATION	EXPECTED DURATION OF IMMUNITY
Yellow fever 17D vaccine, U.S.P. A special strain of living virus attenuated through prolonged cultivation in tissue cultures. Ampules 1 ml. with 10 ml. of diluent, 20 doses. Potency period 12 months. Store below 32° F. (0° C.).	All persons traveling in or through areas where yellow fever is endemic should be given vaccine at least 10 days prior to arrival. See World Immunization Map (Fig. 1) for endemic countries.	Subcutaneous injection of 0.5 ml. of an approximately 1:10 dilution of the concentrated vaccine (freshly prepared). Same dose for children (Table 8). For persons allergic to eggs; see text. If a person can eat eggs, the vaccine may be given.	Six years, or probably longer.
REQUIRED REPEAT INOCULATIONS			COMMENTS
Routine booster of 0.5 ml. of the diluted vaccine 6 years after the initial vaccination if in endemic areas. In the presence of an epidemic, an emergency booster dose of 0.5 ml.			All diluted vaccine which remains unused after 1 hour must be discarded. Yellow fever vaccine should not be given concurrently with cowpox virus, or to persons ill from virus diseases, e.g., influenza. India, Pakistan and Ceylon require vaccine to be given 12 days before arrival.

ache and fever lasting several days.³⁴ Those who are sensitive to egg or chicken protein and are inadvertently given the vaccine can have severe and possibly fatal reactions. In the last 22 years³⁴ outbreaks of encephalitis have occurred following the use of the yellow fever vaccine. This complication is rare, generally manifests itself in children under one year of age^{34, 51} and is mild since no deaths have occurred in the reported cases. In 1960 the first case⁵¹ (a 10 week old infant) believed to occur in the United States appeared in the literature.

Generally speaking, one prefers not to inoculate two live viruses at one time, therefore a 3 week interval between vaccinia and yellow fever inoculations is advised. It has been recommended¹⁰¹ that if yellow fever inoculation is given first, smallpox vaccination can be given 4 days later. However, if smallpox is given first then the 21 day interval is mandatory. In infants under 9 months of age a 3 week interval is maintained regardless which vaccination is given first. If there is evidence of previous successful vaccination against smallpox, yellow fever immunization and revaccination against smallpox may be given concurrently.

In Africa under circumstances of mass immunization, combined smallpox and yellow fever inoculations have been given^{34, 94} successfully and safely, administering the Dakar strain by scarification rather than subcutaneously.⁴¹ In egg-sensitive individuals scarification affords some protection with the 17D vaccine.²⁴ Better protection may occur if anti-histamines are given during a course (0.5 ml. total) of endermal (ED) injections of vaccine as follows: 0.1 ml. ED and if no allergic reaction in 2 to 7 days then give 0.2 ml. ED \times 2 at weekly intervals.

GROUP III. DISEASES IN WHICH VACCINATION IS ADVISABLE IN CERTAIN AREAS OR OCCUPATIONAL GROUPS

Since our last review,⁸⁸ vaccines for three diseases, influenza, measles and poliomyelitis, have been developed or so improved that they have been

placed in the first group. There are three diseases, i.e., the zoonoses, in this group for which immunizing procedures are either of regional or occupational interest only, or else have not been developed or established to a point of general use and acceptance. Since other control measures and in most cases antibiotics are effective, use of these vaccines will always be limited. Vaccines for the two viral diseases, adenovirus and mumps,⁴³ are presently under study, therefore, only brief comments will follow.

Adenoviruses

Recent controlled studies by Meiklejohn and Miller have demonstrated the effectiveness (90 per cent) of adenovirus type 7 vaccine against respiratory infections in military units,⁹³ and of type 4 vaccine against pneumonia in naval recruits.⁹⁸ Combined adjuvant influenza and adenovirus (types 4, 7) vaccine was used by Meiklejohn. Significant increases in type 7 antibody titers were noted in 50 per cent of the subjects and no undesirable reactions to the combined vaccine were noted. Although an effective vaccine is available against types 3, 4 and 7, its use in children at present offers very little since these types are of minor importance during childhood.

Mogabgab¹⁰⁰ discussed the problems of upper respiratory illness vaccines and reported upon the effectiveness of a multivalent vaccine in an industrial group. It appears that these vaccines will be used more extensively in selected adult groups because of their potential value. The Armed Forces are presently administering a single dose, 1 ml., of adenovirus trivalent vaccine, to each new recruit upon entry into the service.²

Mumps

Since mumps vaccine was licensed in 1950 its usefulness has been hard to establish. Epidemics are not occurring as in past years in military or college groups, so it is difficult to evaluate the efficacy of the vaccine in man. Mumps is a benign disease, especially in children. But complications such as orchitis (20 per cent), oophoritis (5 per cent) or meningoencephalitis occur in young adults. One disturbing fact is the occurrence in this country of 37 to 55 deaths annually during the past 10 years¹⁰² (mumps is a non-notifiable disease). Although several well controlled trials⁴¹ have shown that the killed vaccine is moderately effective, studies continue in order to define its characteristics.⁴³ Epidemiological effectiveness of a live vaccine was demonstrated by 90 per cent protection of 35,000 preschool children for at least 3 years in the U.S.S.R.¹⁴⁰

Indications for the killed vaccine are few. It is not recommended for healthy children but may be for the nonimmune adolescent or adults in certain circumstances (hospital or military personnel, institutionalized patients or college students.) A skin test (approximately 75 per cent reliable) should be performed before vaccination to exclude those already immune. One-tenth ml. of mumps antigen is injected endermally. An area of erythema, 1.5 cm. or more, in 24 to 36 hours indicates immunity. A pseudopositive reaction may occur in the presence of hypersensitivity to egg protein. This test can be of value in the differential diagnosis of orchitis, parotitis and meningoencephalitis.

The vaccine is contraindicated in egg-sensitive persons, in the presence of tuberculosis or active or debilitating disease. Reactions are mild and do not last more than 24 hours. Neutralizing antibodies form in most patients by the second to third week but decline rapidly in 6 months time. A course⁷⁸ consists of 2 doses of 1 ml. each given subcutaneously at 1 to 4 week intervals followed in 6 to 12 months by a booster of 1 ml. Annual boosters (0.5 to 1.0 ml.) are necessary to maintain immunity. Pooled gamma globulin (GG) is of no value for passive immunization, but hyperimmune GG, 20 ml. intramuscularly, is temporarily effective.¹⁰⁹

Q Fever

In a recent symposium¹¹ on biological warfare, Q fever was discussed as an effective debilitating agent. Since mortality from Q fever is quite low (less than 1 per cent) without treatment but morbidity is prolonged, large military units could be easily inactivated by aerosols just prior to an invasion. The soldier would be a prisoner by the time the diagnosis was made and recovery occurred. This situation could be avoided since a highly effective formalin-killed vaccine (*R. burnetii*) has been developed.^{11, 41} Local reactions are not unusual with occasional sterile abscesses. Systemic reactions are not infrequent, occasionally requiring hospitalization. At present, use of the vaccine is limited to laboratory workers and those in hazardous occupations. Control of Q fever in man depends upon control of the disease in animals, especially those raised for meat and milk.

Rocky Mountain Spotted Fever

Immunization for this rickettsial disease is seldom indicated because of the rickettsiostatic effect of the tetracycline antibiotics.¹⁵⁴ For those whose occupations take them repeatedly into the woods and forests where ticks abound, the vaccine will reduce the severity of the disease.^{2, 41} Laboratory workers exposed to the agent will benefit from inoculations. The usual course consists of 3 subcutaneous injections of 1 ml. of the Cox yolk sac killed vaccine (suspension of *R. rickettsii*) at 7 to 10 day intervals. Children under 12 receive 0.5 ml. Boosters (0.5 ml.) are given annually. Allergy to egg or chick protein contraindicates use of this vaccine.¹

Tularemia

During the past 10 years the incidence (365 to 680 cases annually) of tularemia has exceeded that of tetanus.¹⁰² Even though fatality is low (5 per cent) in untreated cases and negligible with streptomycin therapy, studies continue for a good vaccine because of prolonged morbidity which may occur, and the epidemiological importance that tularemia may assume in biological warfare.¹¹ Immunity to reinfection is not complete and third attacks have been reported.

Recent studies have shown significant protection for man from infection by virulent strains of *P. tularensis* with a live vaccine.²³ A grippelike disease was readily induced in nonvaccinated men by aerosol administration of a viable attenuated vaccine. Streptomycin, given at the earliest indication of systemic disease, promptly controlled these

symptoms. The vaccine produced no serious reactions and gave significant protection against a respiratory dose upon rechallenge.¹³¹ When available this vaccine would be advisable for hunters, butchers and laboratory workers.

GROUP IV. DISEASES FOR WHICH IMMUNIZATION PROCEDURES ARE OF PASSIVE VALUE OR ARE UNDER STUDY

Several diseases in this group at present can be managed only by passive immunization procedures; e.g., infectious hepatitis. Other diseases are included for which vaccines are available, but their value is debatable or use is controversial due to low morbidity and mortality or effective antibiotic therapy.

Anthrax

Owing to the low incidence, 12 to 26 cases annually, during the past 5 years, the results of field trials with purified anthrax antigen have been inconclusive.^{13, 41} When a potent (cell-free antigen) vaccine becomes available it would be recommended for employees handling potentially contaminated industrial raw materials. Preventive measures should include annual inoculation of animals in enzootic areas with an approved spore vaccine.

Brucellosis

In view of the marked decrease in incidence¹⁰⁴ in the past 15 years, from over 6000 cases in 1947 to 636 in 1961, and no more than 6 to 18 deaths annually in the past 10 years, there is little need in this country for active immunization. Most of the cases have occurred in packing house and farm workers, therefore, if a safe or dependable vaccine were available it would be limited to this group. Ultimate control of brucellosis in man depends upon the elimination of disease among domestic animals. Only pasteurized milk from Bang's tested cattle should be consumed. Vaccines are available for immunization of calves. Extensive use of a live vaccine in man has been of value in the U.S.S.R.¹⁴⁸

Dengue Fever

Protection against breakbone fever may be of critical importance to troops and certain workers in tropical areas, especially if mosquito control is impractical. Studies are in progress with 4 "candidate" strains to produce a live attenuated vaccine against type 1 dengue fever. The least virulent of these strains has produced a good antibody response and will be tested for its ability to protect man.⁴³

Infectious Hepatitis

Two antigenic variants causing hepatitis in man are recognized—virus A (IH) associated with infectious hepatitis and virus B (SH) "related" to serum hepatitis. The latter virus transmitted by blood or blood products differs from virus A (IH) in that it produces a more severe course, has a longer incubation period and may result in a poorer prognosis.⁸⁴ Taylor et al.¹⁴⁴ have isolated 3 distinct serological types of culturally similar viruses from cases of hepatitis. These were found in the serum of 5 to 35 per cent of normal persons and over 95 per cent of patients with viral hepatitis. Two serotypes, named Hemovirus, produced hepatitis in volunteer subjects. From studies which began in 1956

Taylor's group has developed a clinical concept that hepatic involvement, especially associated with jaundice and abnormal liver function, is a relatively infrequent complication of a rather common viral infection.

Until a diagnostic antigen is developed and a vaccine becomes available (3 to 5 years), pooled gamma globulin (PGG) must be used to immunize passively individuals exposed to IH virus, but it is of doubtful value against SH virus. Evidence has shown that immune PGG may be effective in preventing or modifying IH when administered as long as 5 weeks after exposure² (within 6 days of expected onset), and confers protection for as long as 8 weeks after inoculation. If the smaller dose of 0.01 ml./lb. is used it is believed that active-passive immunity may result since PGG suppresses symptoms but does not prevent infection. There is no reason why it should not be used in any individual who has had intimate contact (not secondary); however, the disease is so mild in healthy young children that it may be better to allow them to become infected and acquire a natural immunity.⁶² Since PGG reduces the frequency of multiple cases in families, the majority of physicians feel that it should be given to all family contacts. Pooled gamma globulin (Table 15) should be employed for the control of epidemics in children's and military camps and in institutions.

A higher dose,⁸⁵ 0.06 ml./lb., is indicated for: (1) a child or adult subjected to prolonged or continued exposure in a highly endemic area; (2) pregnant or postmenopausal females; (3) patients with pre-existing hepatic disease. If exposure continues the dose is repeated at intervals of 6 to 8 weeks. For certain individuals, such as Peace Corps and military personnel prior to overseas travel to endemic areas, one injection is given prophylactically and repeated in 4 to 6 months.

Gamma Globulin Prophylaxis

Human pooled gamma globulin (PGG) which contains antibodies to several diseases is employed not only to prevent passively or modify the severity of clinical expression of the disease, but in hopes that active immunity will develop under cover of gamma globulin. The effective use of PGG for prophylaxis must be governed by an understanding of the pathogenesis of the disease to be treated. Passive immunization is not always effective especially if therapy is given too late or in inadequate dosage (Table 15).

Since 1 or 2 days are required for maximum serum levels to be obtained after intramuscular injection, PGG must be administered as soon after exposure as possible. Variations in antibody content occur in different batches of PGG, therefore, the immunity produced is variable⁸⁷ except when specific hyperimmune gamma globulin (convalescent) is used. Toxic reactions to PGG given intramuscularly are uncommon (1 per cent) and rarely serious. These include local inflammation and mild systemic reactions, e.g., malaise, fever (low grade) and headache. Glaser⁶⁶ recently discussed the rarity of anaphylactic reactions to gamma globulin.

Modification of the disease is often preferable to complete prevention, therefore a smaller dose or one given late in the incubation period may result in a modified infection. Separate sections in groups I, III and IV

Table 15. Passive Immunization Procedures*

DISEASE	DOSE—QUANTITY AND ROUTE		
	Child	Adult	COMMENT
Botulism	Bivalent hyperimmune antitoxin 10,000 to 100,000 units IV	Same dose as child	Give immediately when diagnosis is suspected. Dilute 1:10.
Infectious hepatitis	Pooled gamma globulin 0.01 ml./lb. body wt. SC or IM	Pooled gamma globulin 0.05–0.06 ml./lb. body wt. SC or IM	Give within 7 days, may protect up to 6 days before onset of disease. Repeat dose in 6–8 weeks if re-exposed.
Measles	To modify: Pooled gamma globulin: 0.02 ml./lb. body wt. SC or IM	To modify: Same dose as child	To prevent: 0.1 ml./lb. body wt. for all infants, chronically ill children. Double dose if over 6 days since exposure.
Mumps	Nonimmune adolescents: 7.5 ml. hyperimmune GG SC or IM	Hyperimmune gamma globulin 20 ml. SC or IM	Give within 10 days of exposure to prevent orchitis.
Pertussis	Hyperimmune gamma globulin 2.5 ml./lb. body wt. SC or IM	None	Give within 10 days of exposure. Repeat dose in 5–7 days if exposure continues.
Rubella	None	Pooled gamma globulin 20 ml. IM	Only to susceptible woman during first 4 months of pregnancy within 1 week of exposure.
Varicella	Pooled gamma globulin 0.2–0.3 ml./lb. body wt. IM within 3 days of exposure Pooled gamma globulin 0.6 ml./lb. body wt. IM	To modify: Same as child To modify: Same as child	High-risk contacts only; i.e., poor health, neonate, eczema, low steroid dosage, ?pregnancy with negative history. Serious-risk contacts: high steroid dosage (recent or present), blood dyscrasias, antimetabolites.

* See text under specific disease for details of management.

discuss immunizing procedures for most of the diseases in Table 15. Varicella¹²⁵ and botulism⁹⁹ are not included due to space limitations.

Leptospirosis

With an average of 12 deaths per year and an incidence of 24 to 71 cases annually during the past decade, little attention has been given to vaccine study in this country. Extensive trials⁴¹ in Europe with killed vaccines have shown good protection in rice-field workers.⁴ Since good personal hygiene, wearing protective clothes and elimination of animal vectors, i.e., rat, dog, are effective control measures, leptospiral vaccines will not be needed for routine use. When required in certain occupational situations, i.e., veterinarians, farmers, abattoir workers, the vaccine must be effective against the dominant local strain.

Rubella

A great advance has been made with the isolation of the rubella virus simultaneously by Weller and Neva in Boston and Parkman et al.¹² at Walter Reed Army Institute of Research. Further studies¹³⁶ have confirmed and extended their findings, and data obtained from epidemiological and volunteer studies have established the agent as rubella virus (RV). Neutralizing antibodies to RV developed in over 90 per cent of these cases.

With development of an effective vaccine and the ability to determine serologically the status of an individual's immunity to rubella, we will be able to offer immunization when it is needed. Only then will we be able to avoid the high incidence (20 per cent) of congenital malformations¹³⁸ which result from the teratogenic effects of the rubella virus during the first 4 months of pregnancy. Meanwhile, as the basic properties of RV are being investigated, passive immunization with PGG is the only procedure available (Table 15); however, every effort should be made to expose children, especially girls, to German measles so that they will acquire the disease at a time when it is mild and inconsequential.

Trachoma

Although the incidence of trachoma in the U.S. is low, some 500 million persons are afflicted in Asia, the Mediterranean littoral and in the Middle East. Even though the sulfonamides and Terramycin are 75 to 90 per cent effective, many individuals do not receive therapy early enough if at all. Some newly isolated strains of trachoma virus have shown varying susceptibility to antibiotics.¹⁴⁹ Since children are more susceptible, a program of trachoma vaccination using a vaccine developed at Harvard School of Public Health was started last year among the Indian children in Phoenix, Arizona.

Phillips¹¹⁰ reviewed the outstanding work of Grayston et al.⁷⁰ whose preliminary field trials have shown some protection with trachoma vaccine in 200 preschool children. Previous studies with aqueous (formalin, and live) and aluminum adjuvant vaccines on 142 volunteer students showed good antibody production and virtually no reaction to 3 types of vaccine. These studies and others are continuing and appear quite promising.

GROUP V. DISEASES FOR WHICH IMMUNIZATION PROCEDURES ARE NOT ADVISABLE

SCARLET FEVER. There is no indication to immunize against erythrogenic toxin. Since penicillin, preferably long acting benzathine penicillin G,* eradicates beta hemolytic streptococci so effectively, little stimulus to develop a vaccine has occurred. Experience with naval recruits⁹⁸ using Bicillin prophylactically to prevent rheumatic fever has been most gratifying. Edsall⁴² mentions the advantage of seeking a streptococcal vaccine against the types most responsible for serious sequelae. In view of the increasing incidence of streptococcal disease, i.e., a threefold rise in the past decade with 338,410 cases in 1961 and over 100 deaths annually during the same period, the need is understandable. Meanwhile greater effort should be made by physicians to diagnose⁹¹ accurately beta hemolytic streptococcal infections and treat them appropriately for 10 days.⁹⁰

ENCEPHALITIS. The principal arthropod-borne virus infections of North America are eastern equine (EEE), western equine (WEE), and St. Louis encephalitis. The latter accounted for most of the 455 cases of encephalitis in the Tampa, Florida, epidemic in 1962. Unfortunately, vaccines are not available for general use although vaccines for both WEE and EEE viruses have been used to protect laboratory workers. Studies continue in this area.²³

TYPHUS. Endemic (murine) and scrub typhus vaccines are not available. Antibiotics and modern insecticides (miticides) are most effective.

BACTERIAL VACCINES. Mixed bacterial respiratory and staphylococcal vaccines have been used for many years with equivocal success, and most studies have lacked control groups.¹³⁷ Hill⁷⁵ in a review of asthma in children stated

* Bicillin (1.2 million units) or Bicillin C-R 600.

that their efficacy was not reliable, but they may be indicated in problem cases. These vaccines are not recommended for general use.

Poison Ivy Vaccines. Oral and injectable preparations were discussed by Hill who stated that it was only occasionally necessary to attempt immunization in children. The only indication for hyposensitization would be when the need for protection is great and exposure is unavoidable. In our experience short-term (7 day) steroid therapy has been ideal in selected cases.

MISCELLANEOUS. The use of such agents as acne, "cold" (oral or parenteral), arthritis or staphylococcus¹²¹ vaccines and the like is not recommended.

SUMMARY AND CONCLUSIONS

1. A review of the status of active and passive immunization procedures available in 1963 has been presented.
2. The more important procedures have been summarized (dose, indications, technique of administration) in 15 tables.
3. A world map is included which indicates the immunizations necessary for those who travel internationally.
4. At present a dozen excellent vaccines are available; however, it appears that they are not being advocated or employed adequately by the medical profession.
5. It is well known that most people will accept immunization especially if their physician so advises. Health education should always be an integral part of medical practice.
6. Morbidity and mortality reports indicate that through lack of immunization significant numbers of people are becoming ill and dying unnecessarily from diseases which are preventable by proper immunization, therefore it is mandatory that all physicians assume the responsibility of administering vaccines to those who need them.

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